To Veronica

STUDIES ON THE SYNTHESIS AND REACTIVITY OF BRIDGEHEAD-FUSED 1,2,3-TRIAZOLES

by

Stephen Connolly, B.Sc.

Thesis presented for the Degree of Doctor of Philosophy

University of Edinburgh 1984

DECLARATION

I declare that this thesis is my own composition, that the work of which it is a record was carried out by myself and that it has not been submitted in any previous application for a Higher Degree.

The thesis describes the results of research carried out in the Department of Chemistry, University of Edinburgh, under the supervision of Dr. G. Tennant between October 1980 and September 1983.

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I am deeply indebted to my supervisor, Dr. G. Tennant, for his constant guidance and encouragement throughout our collaboration.

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Royal Society of Chemistry - Perkin Division.

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Eleventh Scottish Regional Meeting (1982), University of Stirling.

Autumn Meeting (1982), Heriot-Watt University.

ABSTRACT

The subject matter of this thesis is concerned with investigations of the synthesis and reactivity of bridgehead-fused 1,2,3-triazole derivatives. In particular the synthetic usefulness of the products derived by acid-promoted triazole ring cleavage in such heterocyclic systems was investigated. The description of the results obtained in these studies is preceded by a survey of methods commonly employed for the construction of bridgehead-fused 1,2,3-triazoles and an outline of the types of reactivity which these compounds can exhibit.

The reactivity of a series of 3-phenyl-1,2,3-triazolo-[1,5-a]pyrimidines towards protic acids has been studied and it has been shown that in the case of hydrochloric and hydrobromic acid triazole ring scission proceeds smoothly to afford the respective 2-halobenzylpyrimidine derivatives. Attempts to effect this reaction with a variety of other protic acids was largely unsuccessful. The ability of Lewis acids to catalyse triazole ring scission of 3-phenyl-1,2,3-triazolo[1,5-a]pyrimidines was also investigated and it was found that the latter reacted with boron trifluoride-etherate to give triazole cleaved products. The intermediate boron trifluoride-1,2,3-triazolo[1,5-a]pyrimidine adduct in such reactions was successfully isolated but attempts to induce triazole ring cleavage of the complex by heating with a variety of alkali metal salts met with mixed success.

Attempts to synthesise 2-aminobenzylpyrimidines by the reaction of 2-chlorobenzylpyrimidines with aminating reagents were not successful. In contrast it was found that the synthetically useful 2-aminobenzylpyrimidines could be prepared by the

reduction of the corresponding 2-azidobenzylpyrimidines. Acid-catalysed decomposition of the latter compounds also provided a general route to 2-benzoylpyrimidines and the chemistry of these little studied ketones was investigated. However, attempts to use 2-benzoylpyrimidines to prepare novel bicyclic heterocycles failed. 2-Aminobenzylpyrimidines were readily acylated by a variety of acid chlorides and the resulting amides reacted with phosphoryl chloride in 1,2-dichloroethane to give imidazo[1,5-a]-pyrimidine derivatives. The scope of this two-step acylation-cyclisation procedure was investigated in detail and provides a general route to the little studied imidazo[1,5-a]pyrimidine nucleus.

1,2,3-Triazolo[1,5-a]-1,3,5-triazine derivatives were prepared and the reactivity of this virtually unknown ring system towards acid-promoted triazole cleavage was investigated. In many cases such scission proceeded smoothly and provided a new route to 1,3,5-triazine derivatives. Attempts to synthesise imidazo[1,5-a]-1,3,5-triazines failed due to the instability of the 2-azidobenzyl-1,3,5-triazines required as precursors of the key intermediate 2-aminobenzyl-1,3,5-triazines.

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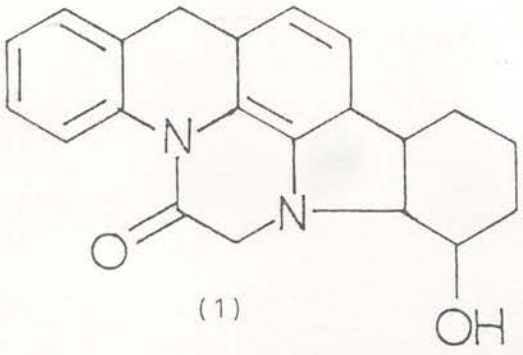
Chapter 1

INTRODUCTION

A Review of the Synthesis and Reactivity of Bridgehead-fused 1,2,3-Triazole Derivatives



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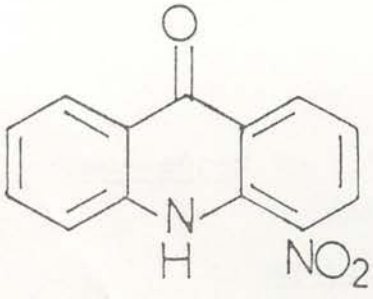

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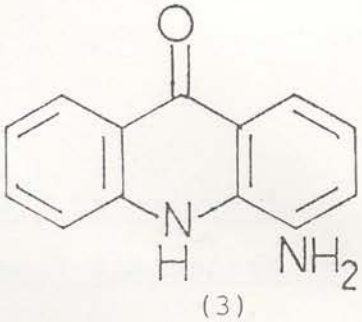

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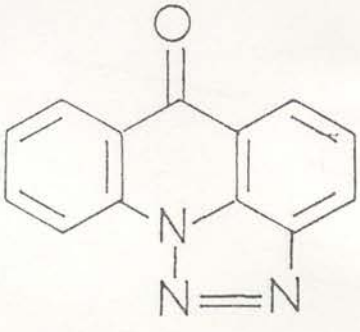

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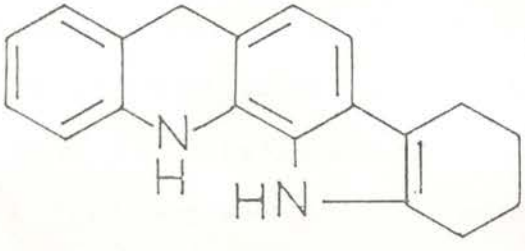
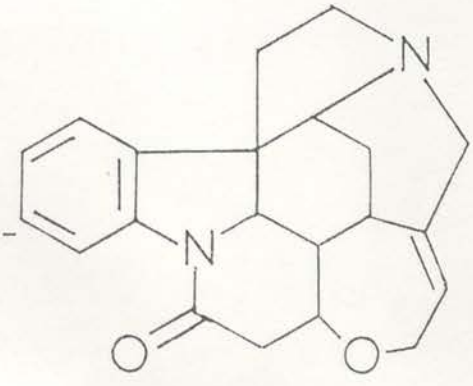


(5)

(i) $(NH_4)_2S$

(ii) $H_2SO_4/NaNO_2$

(iii) Zn/AcOH; cyclohexanone



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Scheme 1

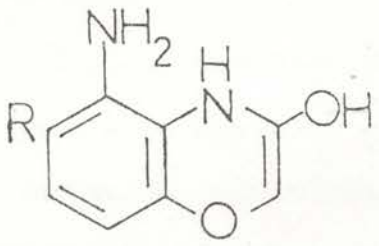
1.1 Introduction

The following thesis is concerned with studies of the synthesis of various bridgehead-fused 1,2,3-triazolo heterocyclic ring systems, their reactivity towards triazole ring scission and the synthetic utility of the products of such ring cleavage. To place the thesis in context the detailed discussion in chapters 2-4 of the results obtained is preceded in chapter 1 by a survey of known methods of bridgehead-fused 1,2,3-triazole synthesis and the more common reactions that such heterocycles undergo.

1.2 A Review of the Synthesis and Reactivity of Bridgehead-fused 1,2,3-Triazole Derivatives

In 1924 while working on a synthesis (Scheme 1) of what was then thought to be the structure of strychnine (1) Clemo, Perkin and Robinson[1] isolated what appears to be the first example of a bridgehead-fused 1,2,3-triazole derivative (4). Thus, on reduction of 9-nitroacridone (2) with ammonium sulphide[2] and treatment of the resulting amine (3) with nitrous acid, the triazole (4) was obtained and called 'acridonediazole'. When this 6H-1,2,3-triazolo[4,5,1-mn]acrid-6-one (4) was treated with zinc dust and acetic acid in the presence of cyclohexanone the pentacyclic compound (5), a presumed precursor of the compound (1), was formed. However it was only much later that strychnine was shown[3,4] by X-ray crystallography to have the more complex bridged structure (6).

Over the next fifteen years examples of bridgehead-fused 1,2,3-triazoles were still very rare[5]. Two groups of workers



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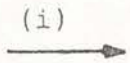
(i) $HCl/NaNO_2$



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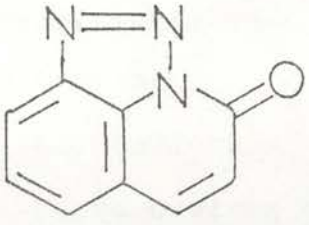
R

a; H

b; $AsO(OH)_2$

Scheme 2



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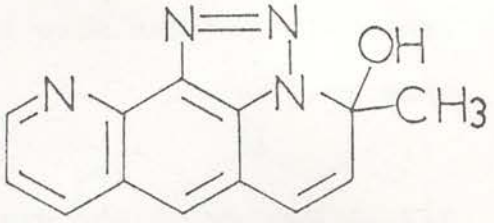

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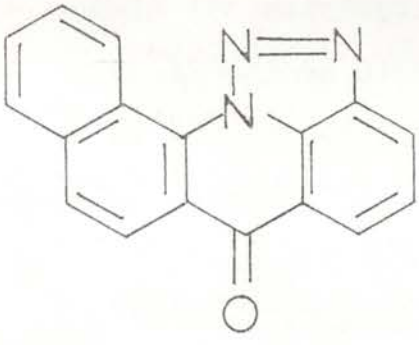

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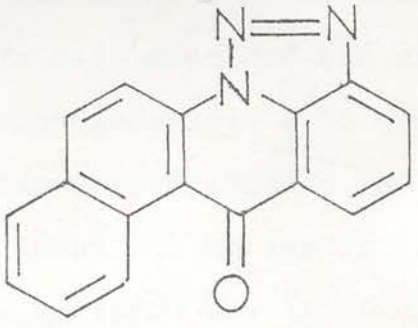

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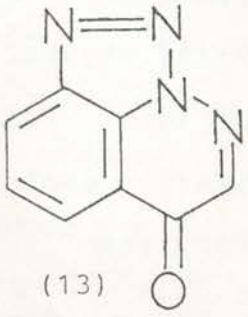
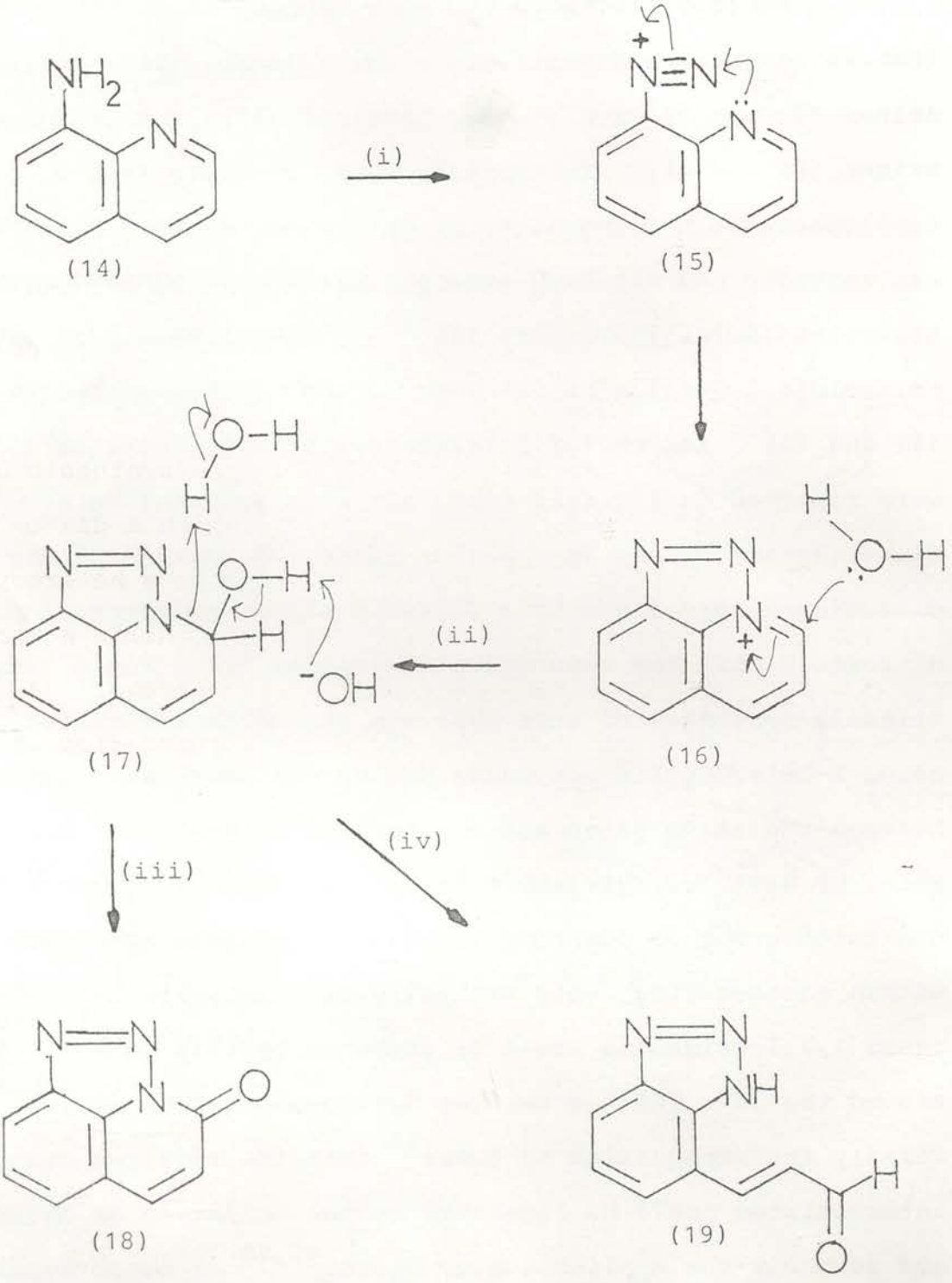


(13)

Scheme 3

Kehrmann and Rohr[6] in 1927 and Lehmstedt and Schrader[7] ten years later reported further examples of the triazoloacridine ring system [c.f.(4)] while in 1928 Newbery *et al* [8,9] showed (Scheme 2) that on diazotisation the 5-amino-3-hydroxybenzoxazines (7a and b) gave the 1,2,3-triazolo[1,5,4-de]-1,4-benzoxazines (8a and b). Thereafter, until the late 1950's, development of the chemistry of bridgehead-fused 1,2,3-triazoles was sporadic and although examples (Scheme 3) of 4H-1,2,3-triazolo[4,5,1-ij]quinoline (9)[10-12], 4H-pyrido[3,2-g]1,2,3-triazolo[4,5,1-ij]quinoline (10)[13], the benzotriazoloacridines (11 and 12)[14] and 6H-1,2,3-triazolo[4,5,1-ij]cinnoline (13)[15] were reported during this time, all were synthesised by diazotisation of the appropriate amine and capture of the diazonium-intermediate by a suitably placed heterocyclic nitrogen within the same molecule (Scheme 3). Fused 1,2,3-triazole syntheses of this type are therefore restricted to amino-*N*-heterocyclic compounds having the correct relationship between the amino group and a heterocyclic *N*-atom. Furthermore, because 1,2,3-triazole formation takes place between a diazonium group on one ring and a nitrogen atom contained within another ring, only tricyclic or polycyclic bridgehead-fused 1,2,3-triazoles could be prepared by this method. However around the late fifties two key developments took place. Firstly the recognition by Bower[16] that the required diazo-intermediates could be furnished by the oxidation of hydrazones and secondly the application by Regitz[17,18] of diazo-transfer reactions in the synthesis of bridgehead-fused 1,2,3-triazoles. Since then further advances in the chemistry of bridgehead-fused 1,2,3-triazoles have taken place as a result of synthetic



(i) HONO

(ii) H_2O

(iii) $KMnO_4$

(iv) OH^-

Scheme 4

approaches based upon cycloaddition reactions of azides and condensation reactions of preformed 1,2,3-triazoles.

All of the synthetic methods for bridgehead-fused 1,2,3-triazoles will now be discussed in more detail and thereafter the varied reactivity of bridgehead-fused 1,2,3-triazoles will be described.

1.3 Synthetic Routes to Bridgehead-fused 1,2,3-Triazoles

1.3.1 Cyclisations involving the generation and capture of a diazo species

The most commonly described method for the synthesis of bridgehead-fused 1,2,3-triazoles is that in which a diazo-species is generated in a β-position relative to a heterocyclic nitrogen atom and cyclisation occurs via nucleophilic attack by the heterocyclic nitrogen atom on the diazo-group. A variety of methods are now available for the generation of such systems.

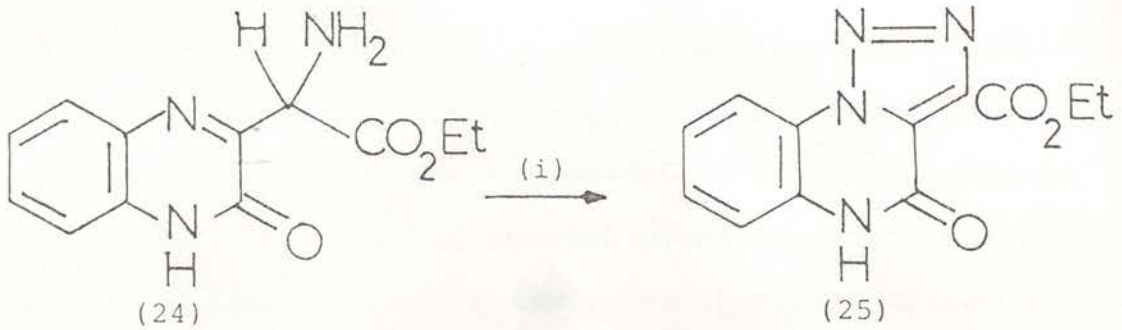
(a) Generation of the diazo-species by diazotisation of amino groups

As previously described all of the early work leading to bridgehead-fused 1,2,3-triazoles employed this method[1,5-15] and it has continued to be used to provide polycyclic triazoles.[19,20] For example (Scheme 4) El'tsov and his co-workers[19] have diazotised 8-aminoquinoline (14) to generate the diazonium cation (15). Nucleophilic attack by the heterocyclic nitrogen atom on the diazo-group in the latter gave the triazole cation (16) which reacted with solvent to produce 4H-4-hydroxy-1,2,3-triazolo[4,5,1-ij]quinoline (17). Potassium permanganate oxidation subsequently gave the 4H-1,2,3-triazolo-

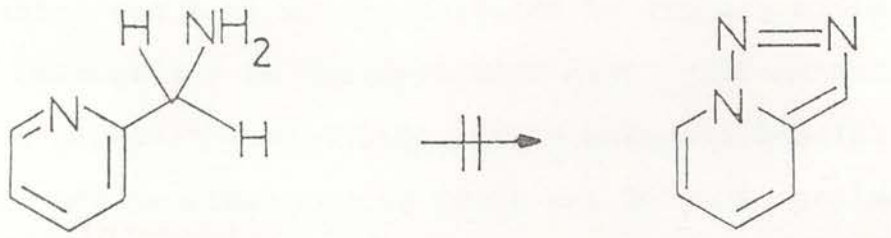
[4,5,1-ij]quinol-4-one (18). It is also reported[19] that in alkaline media the 4-hydroxytriazoloquinoline (17) is isomerized to the β-(7-benzotriazolyl)acrolein (19) presumably via the mechanism shown (Scheme 4).

While studying the kinetics of ring closure in fused [4,1]oxazepin-5-ones Barlow *et al* [21] extended the diazo-trapping method to allow capture of the diazo-group by a non-heterocyclic nitrogen (Scheme 5). Thus diazotisation of the diamino compound (20) and trapping of the diazonium intermediate (21) with concomitant loss of the amino proton produced the initially non-bridgehead-fused benzotriazole (22). Subsequent closure of the oxazepinone ring provided the 7H-4,5-dihydro-1,2,3-triazolo[4,5,1-jk]4,1-benzoxazepine derivative (23) (Scheme 5).

Attempts to synthesise bridgehead-fused 1,2,3-triazoles by diazotisation of primary alkylamines (as opposed to aryl-amines) have met with mixed success. For example (Scheme 6) although Chapman has reported[22] that the aminoalkylquinoxalinone (24) when diazotised produced the 1,2,3-triazolo[5,1-a]quinoxalin-4(5H)-one (25) it has also been found[23,24] that none of the 1,2,3-triazolo[1,5-a]pyridine (27) was formed on diazotisation of the aminomethylpyridine (26). It is important to recognise the difference in this approach to that of the earlier work in which the species being trapped was an aryldiazonium cation. In the above examples diazotisation of a primary alkylamine (28) gives an alkyldiazonium cation (29). This has the choice of losing a proton to form a diazoalkyl species (30) which could then be trapped by the heterocyclic nitrogen atom to provide a bridgehead-fused 1,2,3-triazole compound (31).

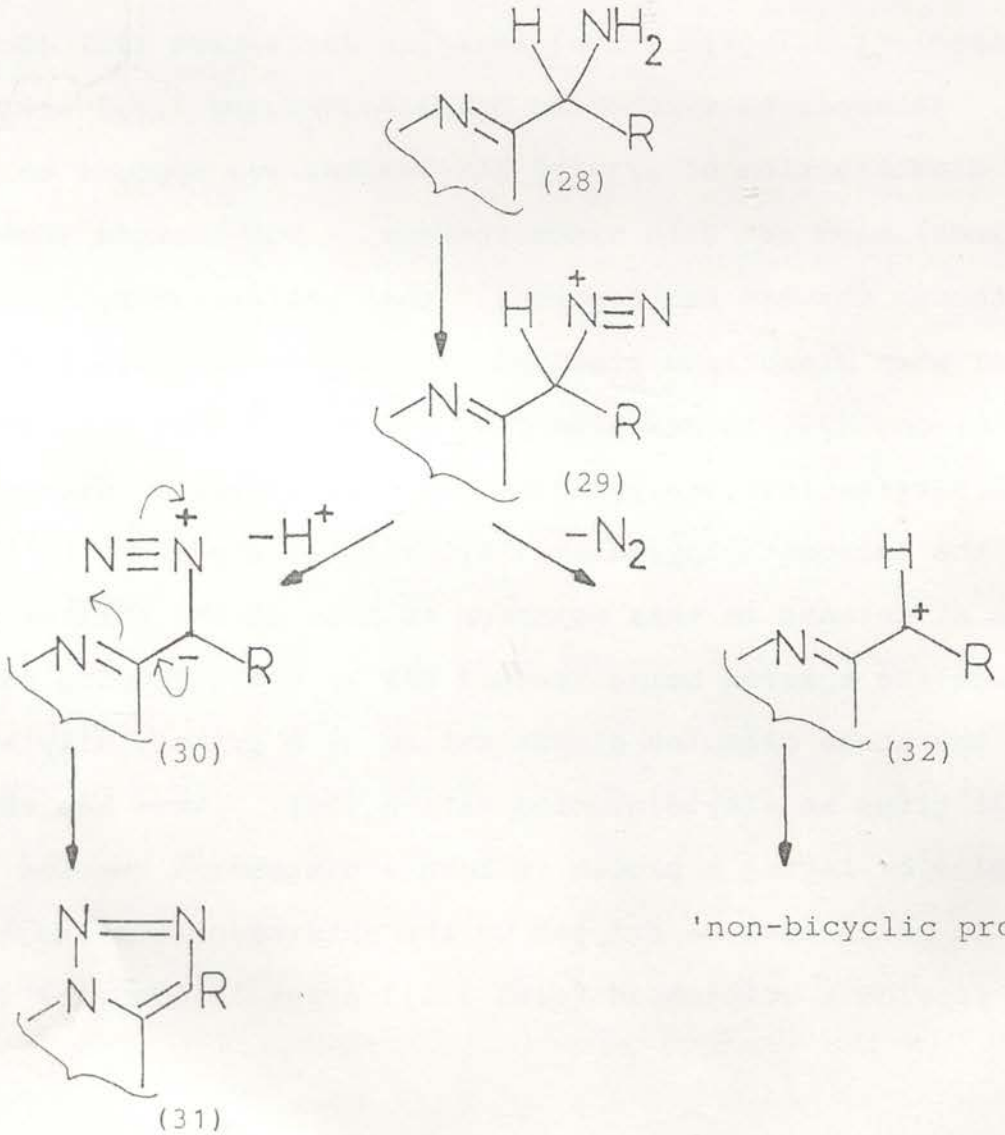


(24) (25)



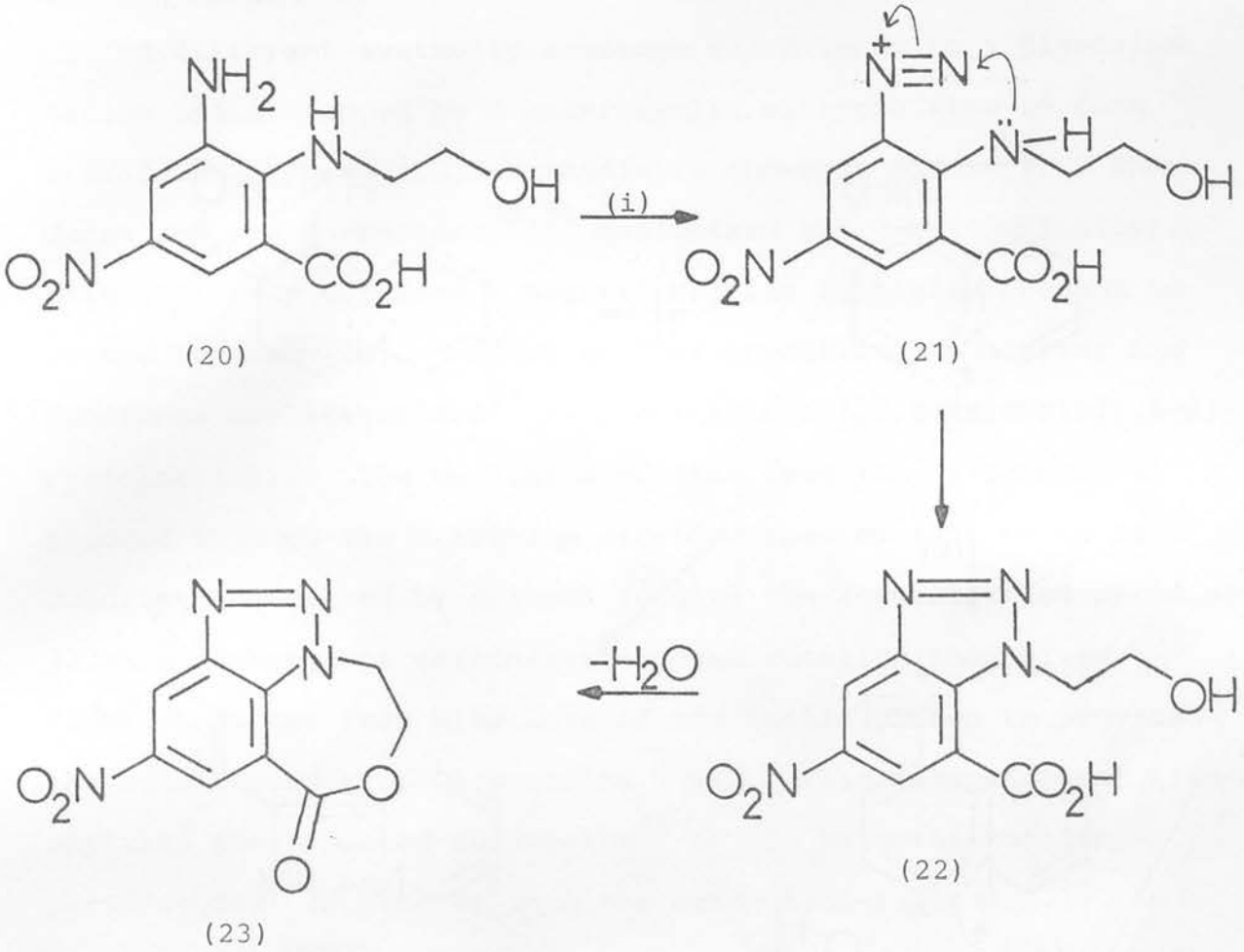
(26) (27)

(i) AcOH/isopentyl nitrite



'non-bicyclic products'

Scheme 6

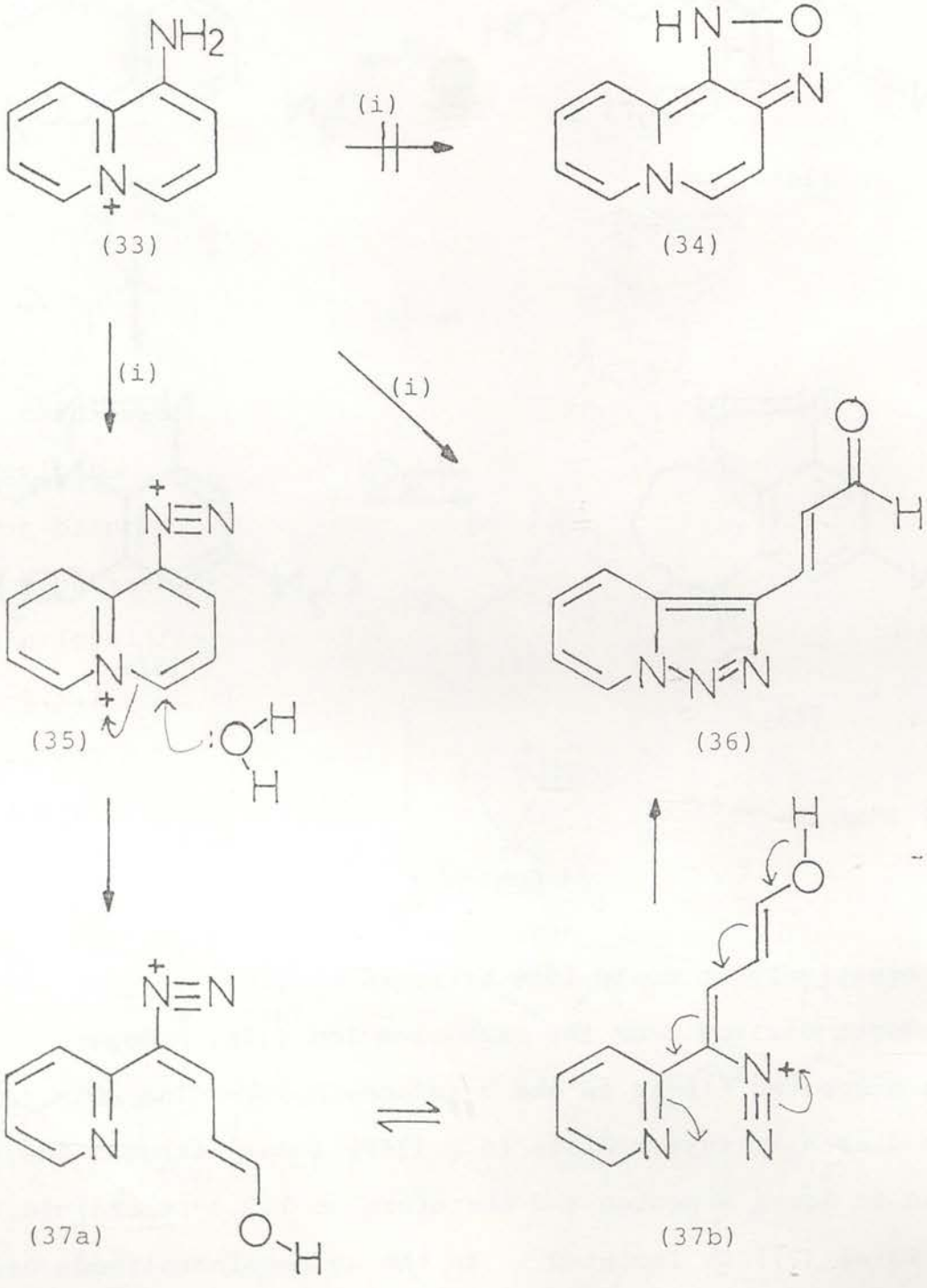


(20) (21) (22) (23)

(i) HONO

Scheme 5

Alternatively it could lose nitrogen to give non-bicyclic products derived from the carbonium ion (32). Boyer has suggested[23] that in the 2-aminomethylpyridine case (26) the diazonium intermediate [e.g.(29)] loses nitrogen faster than it loses a proton and therefore no 1,2,3-triazolo[5,1-a]-pyridine (27) is isolated. In the aminoquinoxalinone case the electron-withdrawing ethoxycarbonyl group would enhance the rate of proton loss to produce a neutral diazoalkyl species and allow the 1,2,3-triazolo[5,1-a]quinoxalin-4(5H)-one (25)

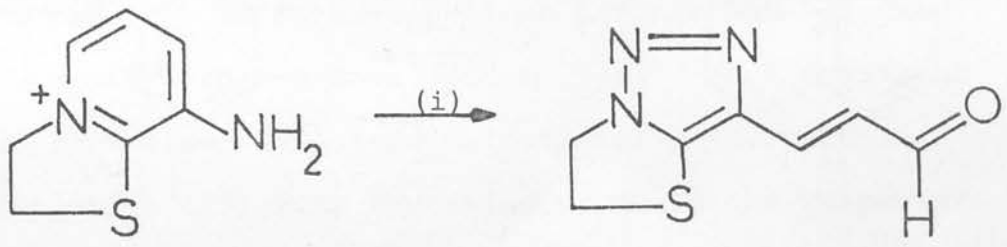


(i) dilute $HCl/NaNO_2$

Scheme 7

to be obtained.

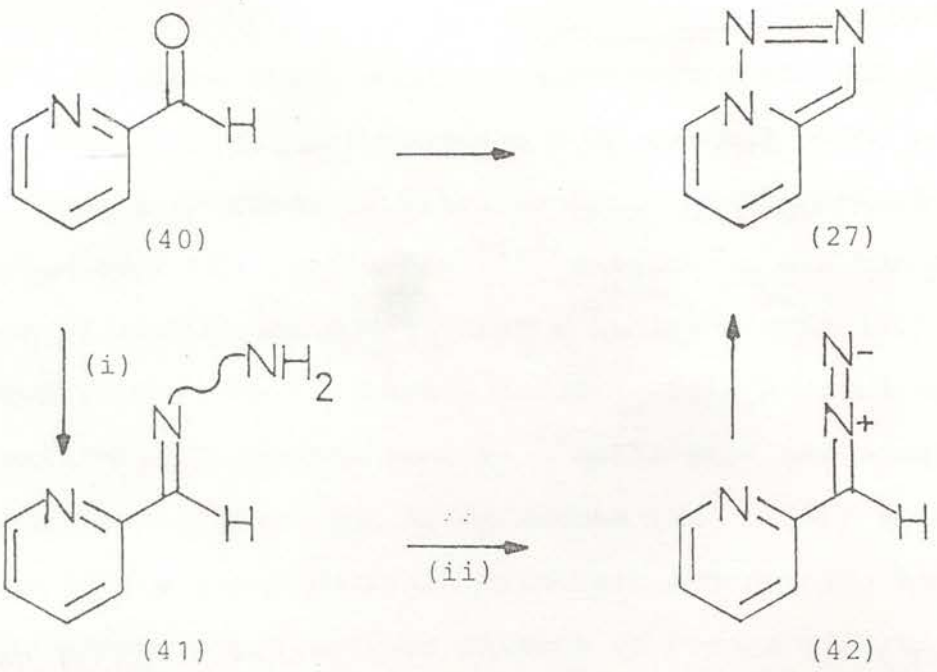
A different synthetic sequence which leads to a diazonium cation being trapped by a heterocyclic nitrogen atom to form a bridgehead-fused 1,2,3-triazole is shown in Scheme 7. When Jones and his co-workers[25,26] diazotised the 1-aminoquinolizium salt (33) they obtained a neutral species initially thought to be the furazan (34). After further investigation however the substance was identified[27] as 3-acroleinyl-1,2,3-triazolo[1,5-a]-pyridine (36). The mechanism of this reaction is thought to proceed through the diazonium dication species (35) which is readily ring opened by solvent to give the 2-substituted pyridine (37a). Subsequent carbon-carbon bond rotation then gives (37b) which cyclises with loss of the enolic proton to provide the substituted triazolopyridine (36). This rearrangement also explains the reported conversion[28] of the aminothiazolidino-pyridine (38) (Scheme 8) into the bridgehead-fused 1,2,3-triazolothiazolidine (39) and has precedent in the reaction of 3-aminopyridinium cations with nitrous acid to give acrolein-substituted triazoles.[29,30]



(38) (39)

(iii) AcOH/isopentyl nitrite

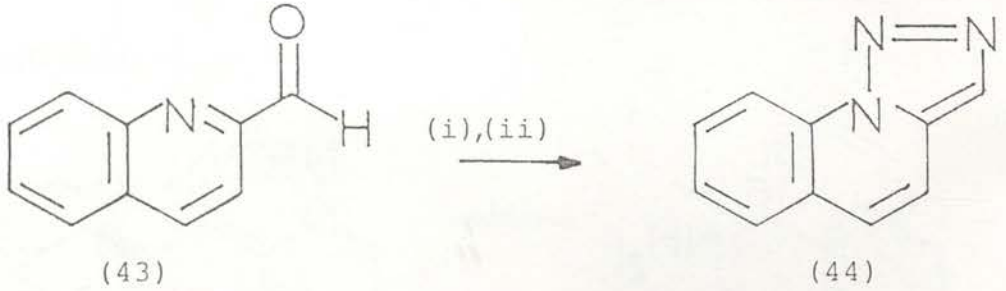
Scheme 8



(i) NH_2NH_2

(ii) Ag_2O

Scheme 9



(i) NH_2NH_2

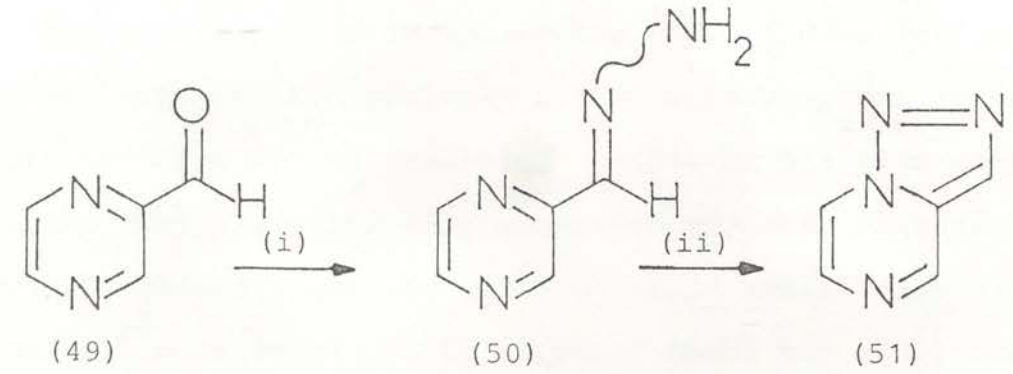
(ii) Ag_2O or MnO_2

Scheme 10

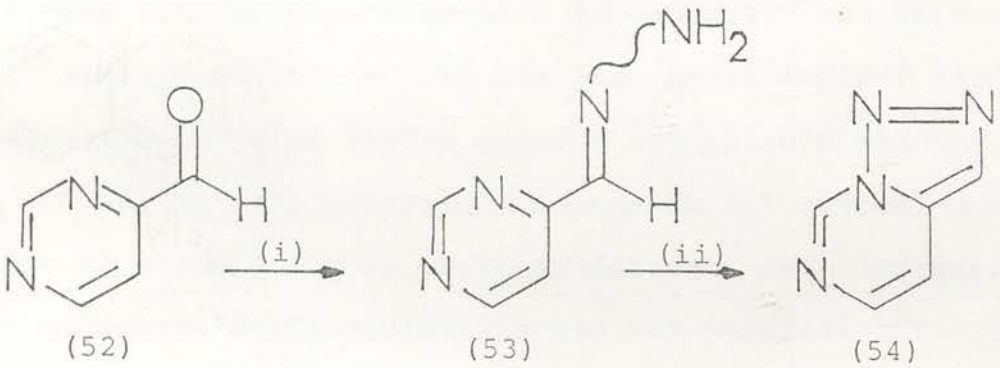
(b) Generation of the diazo-species by oxidation of hydrazones

In 1957 both Bower[16] and Borger *et al*[23] demonstrated (Scheme 9) the synthesis of 1,2,3-triazolo[1,5-a]pyridine (27) from 2-formylpyridine (40). Treatment of the aldehyde (40) with hydrazine gave the hydrazone (41) which was then oxidised directly with silver oxide to give, via the transient diazo-compound (42), the fused triazole (27). Boyer *et al*[31] also utilised this route to provide other examples of bridgehead-fused 1,2,3-triazoles. For example (Scheme 10) silver oxide oxidation of the hydrazone of 2-formylquinoline (43) gave 1,2,3-triazolo[5,1-a]quinoline (44) and it has also been shown[32,33] that manganese dioxide can equally effect this transformation. Treatment (Scheme 11) of the bis-hydrazone (46) of the di-pyridylglyoxal (45) with silver oxide gave a product to which Boyer *et al*[23] assigned the bis-triazolopyridine structure (47) and although at that time these workers could not rule out the alternative isomeric structure (48) this was excluded later[34] [see part (c); page 10].

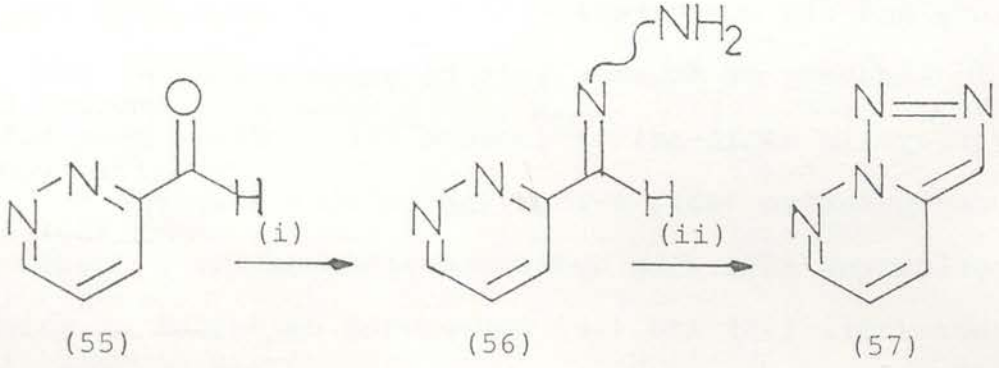
Maury and his co-workers[35,36] have also exploited the synthetic strategy of Schemes 9-11 to prepare some of the simpler bicyclic azolo-azines (Scheme 12). Thus treatment of 2-formylpyrazine (49), 4-formylpyrimidine (52) and 3-formylpyridazine (55) with hydrazine produced the respective hydrazones (50), (53) and (56) subsequent oxidation of which with lead tetraacetate afforded 1,2,3-triazolo[5,1-a]pyrazine (51), 1,2,3-triazolo[5,1-c]pyrimidine (54) and 1,2,3-triazolo-[5,1-b]pyridazine (57). The latter ring system has also been



(49) (50) (51)



(52) (53) (54)

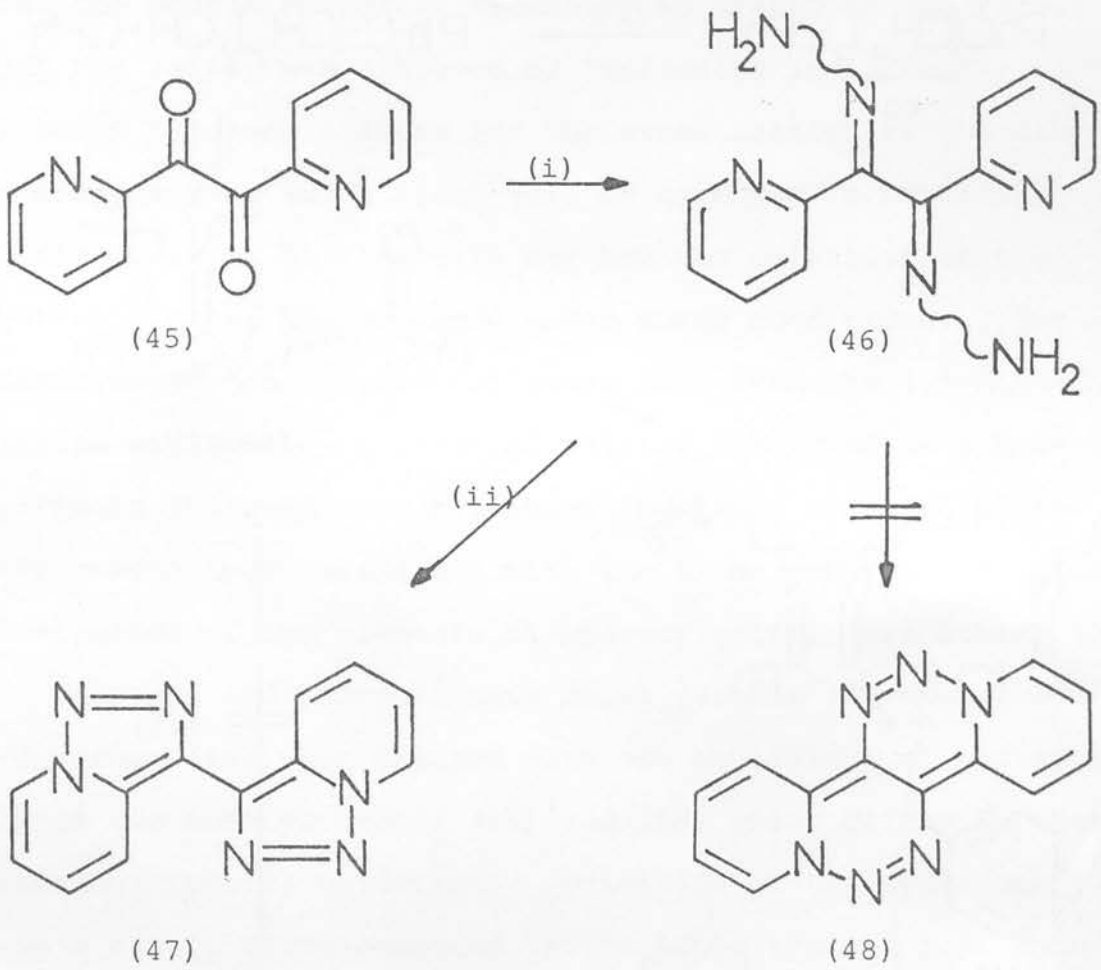


(55) (56) (57)

(i) NH_2NH_2

(ii) $Pb(OAc)_4$

Scheme 12



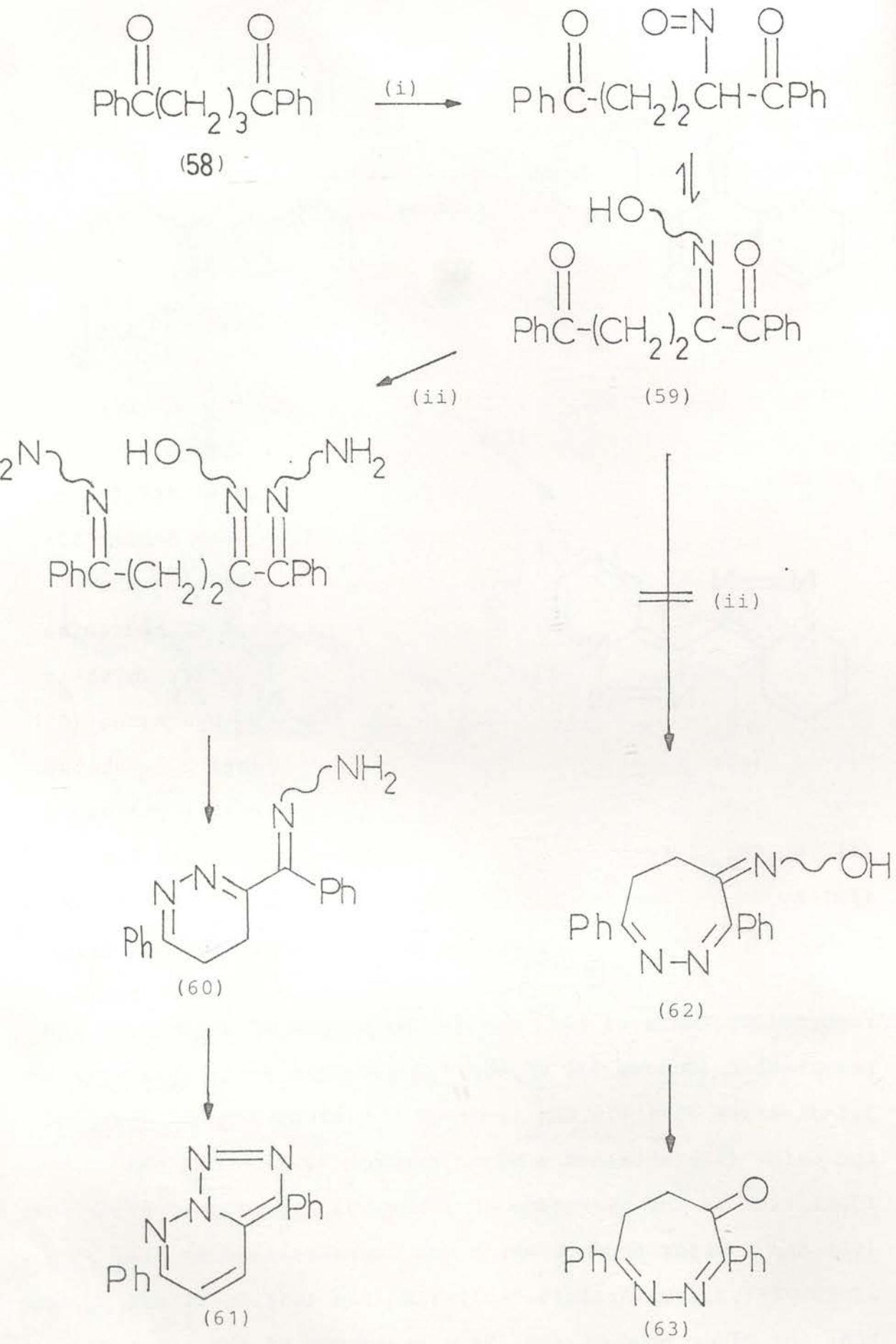
(45) (46) (47) (48)

(i) NH_2NH_2

(ii) Ag_2O

Scheme 11

reported by Evans *et al*[37] who in the course of attempting the preparation (Scheme 13) of the 1,2-diazepin-4-one (63) from the 1,5-diketone (58) via the tautomeric nitroso product (59) and the oxime (62) obtained a minor product (22%) which was identified as the hydrazone of 3-benzoyl-4,5-dihydropyridazine (60) and a major product which was characterised as 3,6-diphenyl-1,2,3-triazolo[5,1-b]pyridazine (61). It was proposed[37] that the minor product (60) is a precursor of the major and



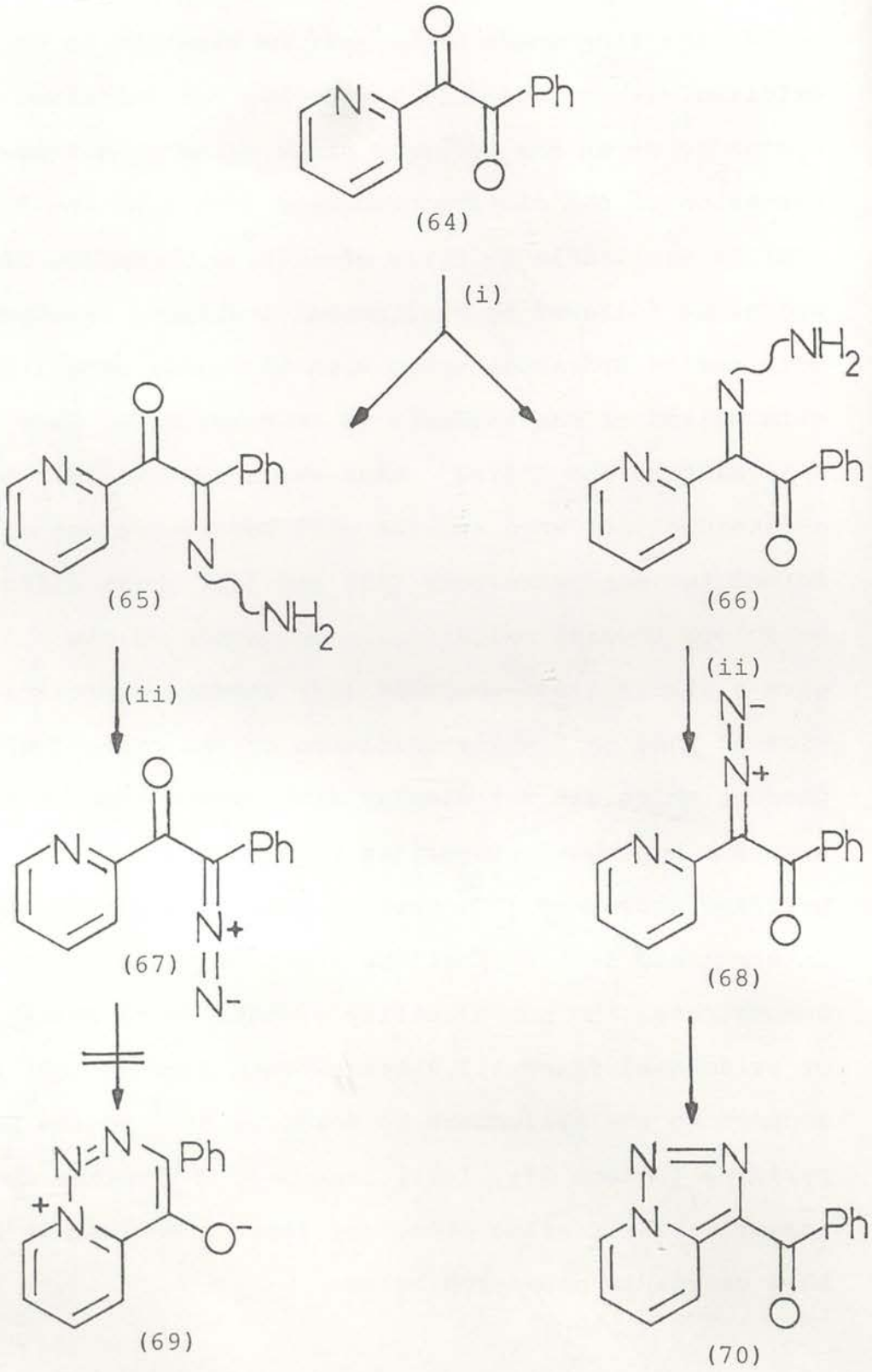
(i) NaOEt/butyl nitrite

(ii) NH_2NH_2

Scheme 13

that the double oxidation necessary to transform the former into the latter was achieved by 'refluxing in solvent'. Although this may account for the aromatisation of the dihydropyridazine ring which might well be expected to be easily oxidised, it is difficult to see how the oxidation of the hydrazone group has occurred under these conditions. The formation of the dihydropyridazine (60) from the 1,5-diketone (59) is explicable in terms of initial formation of a bis-hydrazone followed by cyclisation involving reaction of the more remote hydrazone group with the oxime substituent (with elimination of the elements of hydroxylamine) (see Scheme 13).

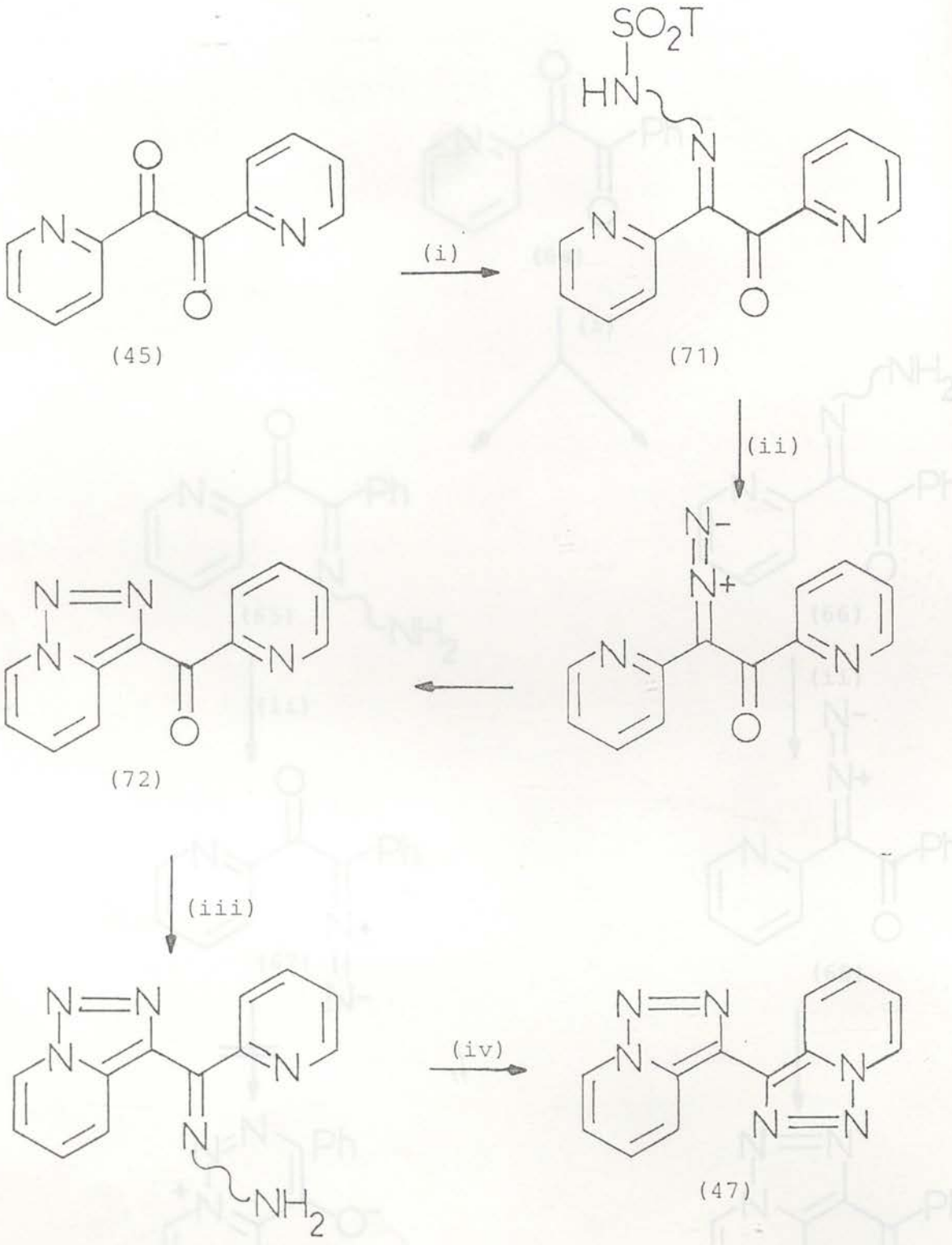
Eistert and Endres[38] have shown (Scheme 14) that the α-diketone (64) when treated with one equivalent of hydrazine formed two monohydrazones (65) and (66) which differ in their behaviour towards oxidation. Oxidation of the hydrazone (65) gave a stable diazo-compound (67) showing typical i.r. absorption at 2100 cm^{-1} while oxidation of the other (66) yielded a product which did not display diazo-absorption in its i.r. spectrum and whose properties were consistent with the triazolopyridine structure (70) derived from cyclisation of the diazo-intermediate (68). That the diazo-compound (67) was stable demonstrates the non-viability of this route for the preparation of bridgehead-fused 1,2,3-triazinones such as (69) and lends support to the assignment by Boyer *et al*[31] of the bis-triazolopyridine [Scheme 11; (47)] (see page 7) rather than the isomeric bis-triazine structure (48). Further evidence to this effect is presented below.



(i) NH_2NH_2

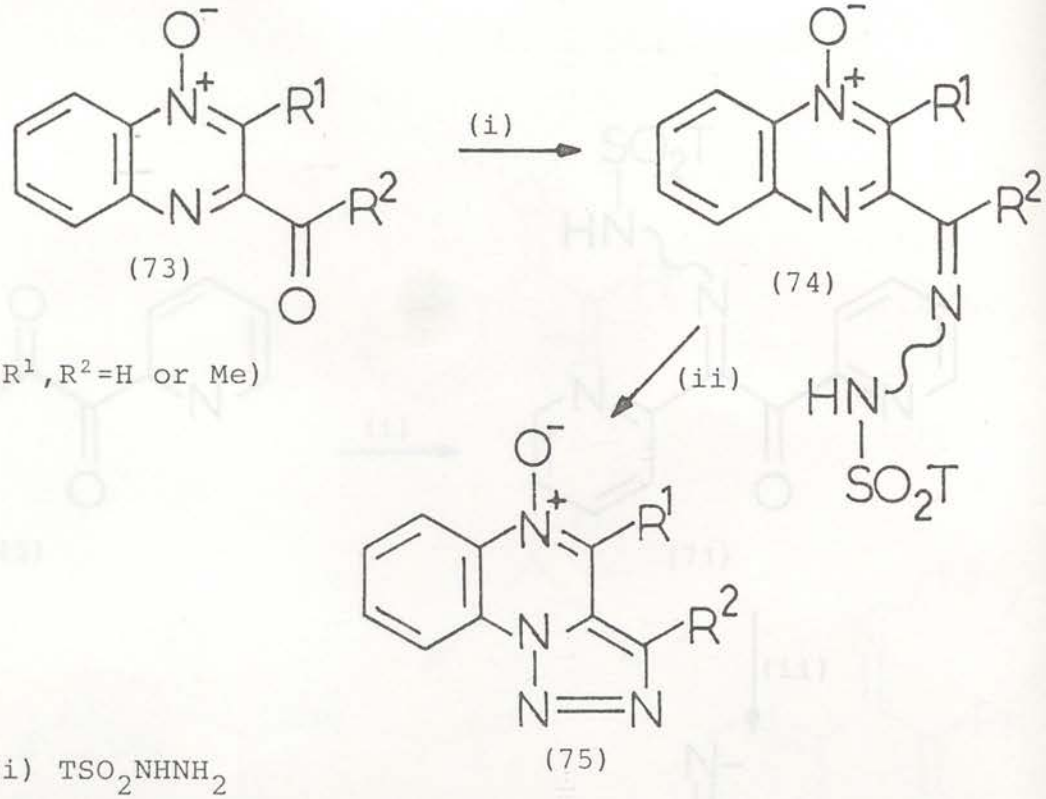
(ii) Ag_2O

Scheme 14



(i) TSO_2NHNH_2
(ii) NaOMe
(iii) NH_2NH_2
(iv) Ag_2O

Scheme 15



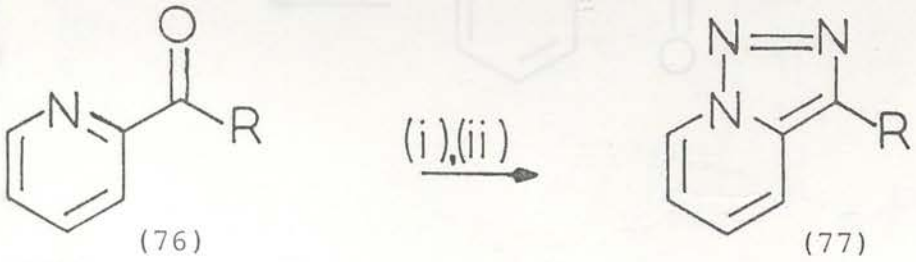
(73) (74) (75)

(R^1,R^2=H or Me)

(i) TSO_2NHNH_2

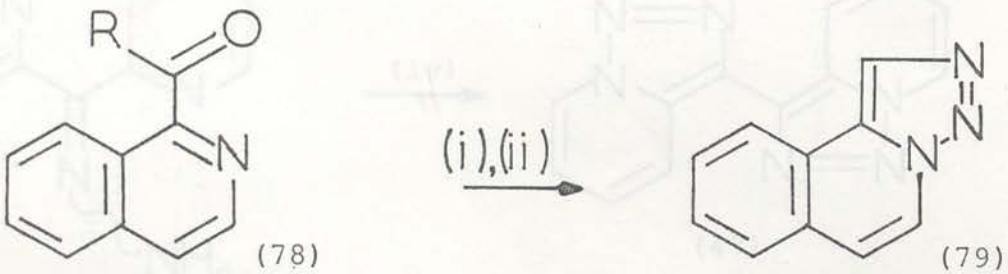
(ii) NaOMe

Scheme 16



(76) (77)

(R=Ph or 2-pyridyl)



(78) (79)

(R=H, Me or Ph)

(i) TSO_2NHNH_2

(ii) NaOMe

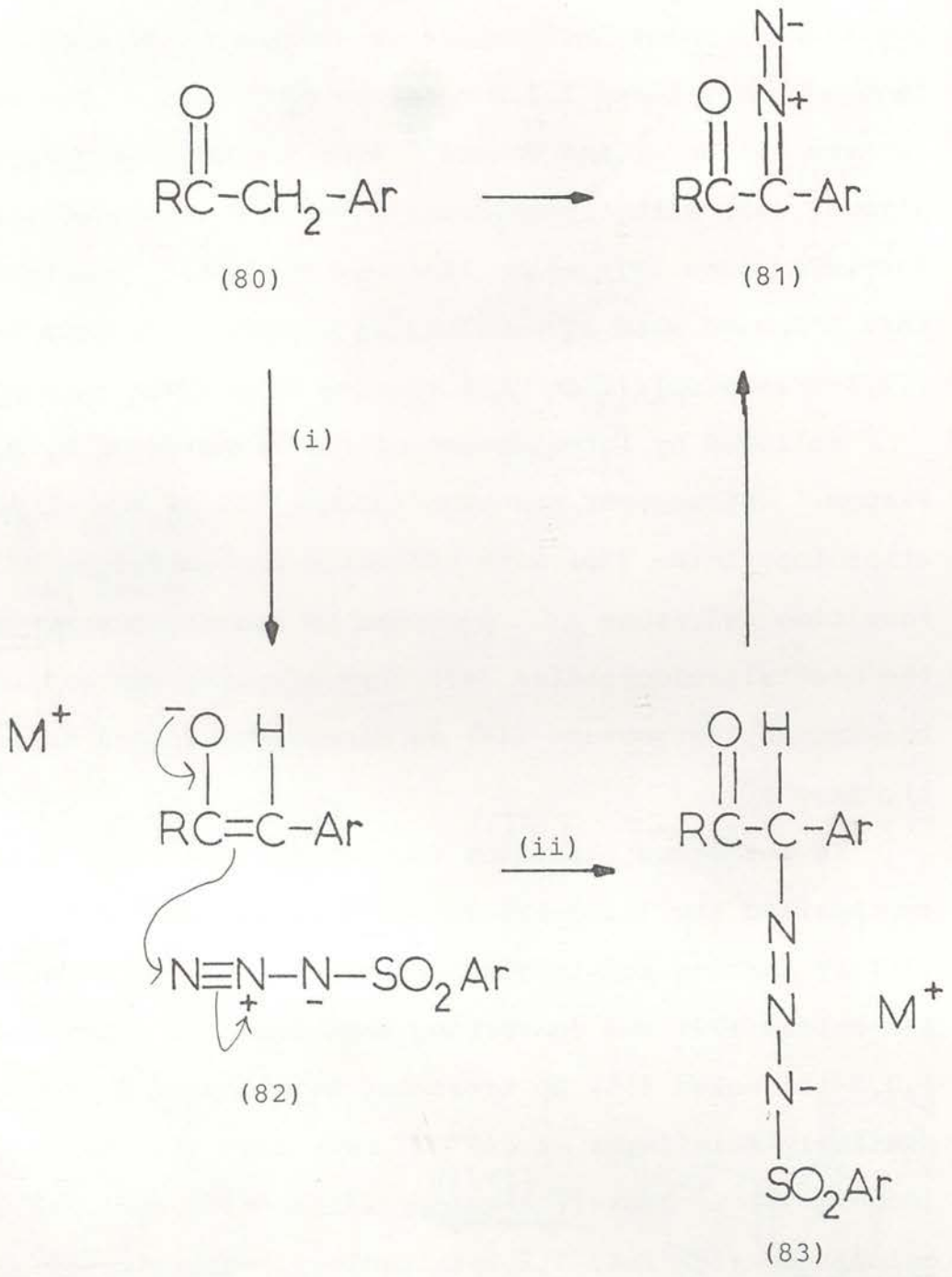
Scheme 17

(c) Generation of the diazo-species by base-catalysed decomposition of tosylhydrazones

Several workers[32-34,39] have used base-catalysed decomposition of *p*-tosylhydrazones as the source of diazo-intermediates in bridgehead-fused 1,2,3-triazole syntheses. For instance (Scheme 15) Boyer and Goebel[34] have treated the di-pyridylglyoxal (45) with tosylhydrazine thereby obtaining the monotosylhydrazone (71) as an isolable product. Treatment of this compound with aqueous alkali converted it into 3-picolinoyl-1,2,3-triazolopyridine (72) via the open-chain diazo-intermediate

followed by interception of the diazo-group by the pyridine *N*-atom. Subsequent reaction (Scheme 15) of the picolinoyltriazolopyridine (72) with hydrazine and oxidation of the resulting hydrazone provided an unambiguous synthesis of the bis-triazolopyridine (47) thus allowing the exclusion of the isomeric structure (48) as already discussed (see Scheme 11, page 7).

In analogous reactions (Scheme 16) Cue *et al*[39] have synthesised the 1,2,3-triazolo[5,1-a]quinoxaline 5-N-oxides (75) by forming the tosylhydrazones (74) of the 2-acylquinoxaline 4-N-oxides (73) and converting them into the bridgehead-fused 1,2,3-triazoles (75) by treatment with sodium methoxide. Similarly Reimlinger *et al*[32,33] have used this synthetic method (Scheme 17) to convert 2-acylpyridines (76) and 1-acylisoquinolines (78) into 1,2,3-triazolo[1,5-a]pyridines (77) and 1,2,3-triazolo[5,1-a]isoquinolines (79).



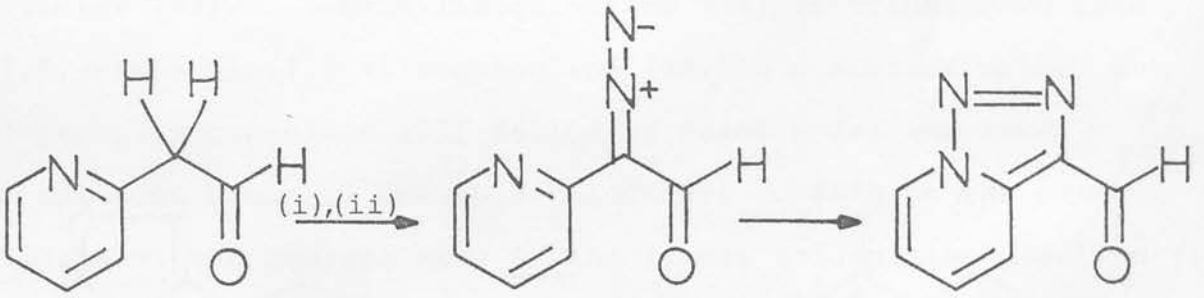
(i) Base

(ii) $ArSO_2N_3$

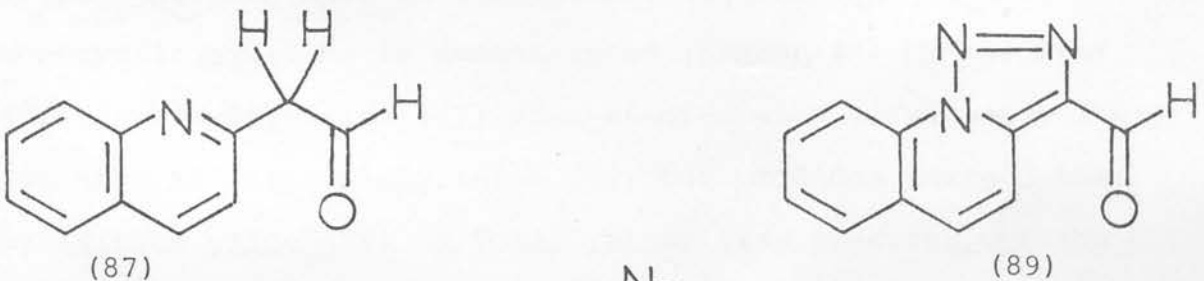
Scheme 18

(d) Generation of the diazo-species by diazo-transfer reactions

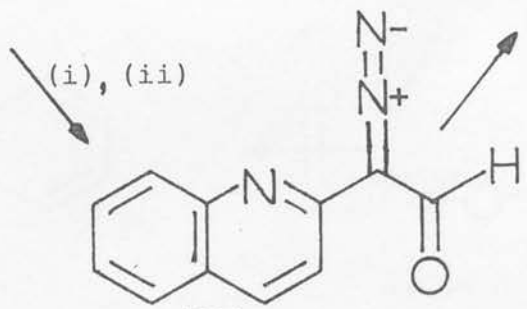
In the early 1960's Regitz[40,41] had been investigating the reactions of active methylene compounds with organic azides when he discovered that by using a sulphonyl azide a diazo-group could be transferred to the position α to a carbonyl group. Thus treatment (Scheme 18) of keto-compounds such as (80) with base to generate the anion (82) followed by addition of an arylsulphonyl azide gave the α-diazo-carbonyl compounds (81). An arylsulphonamide was the by-product in this reaction and the mechanism is considered to involve an adduct such as (83). On extension (Scheme 19) of such diazo-transfer reactions



(84) (85) (86)



(87) (89)

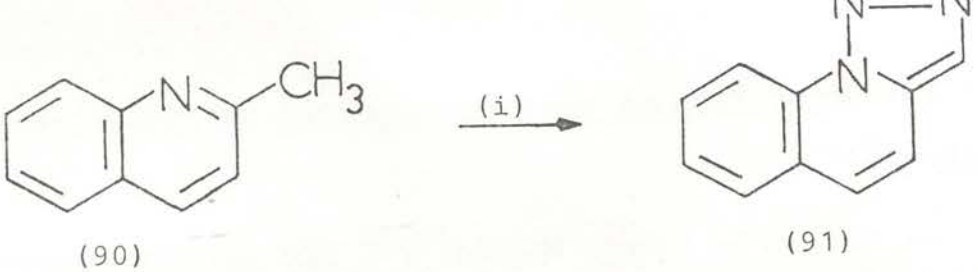


(88)

(i) KOEt

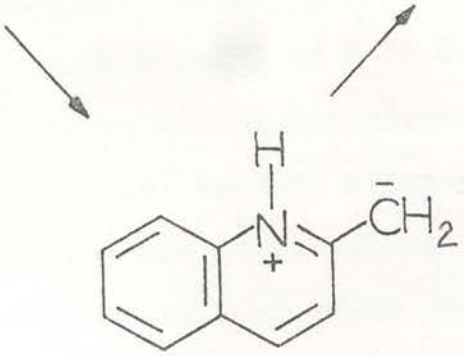
(ii) $ArSO_2N_3$

Scheme 19

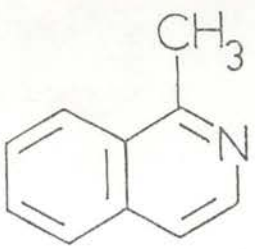


(90)

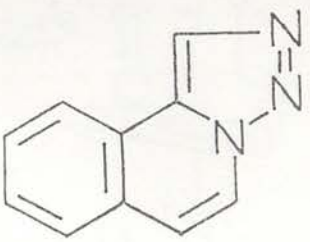
(91)



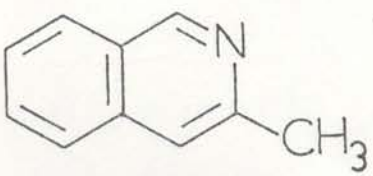
(92)



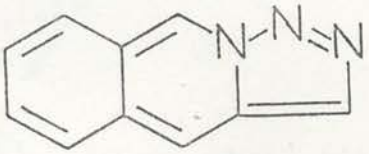
(93)



(94)



(95)



(96)

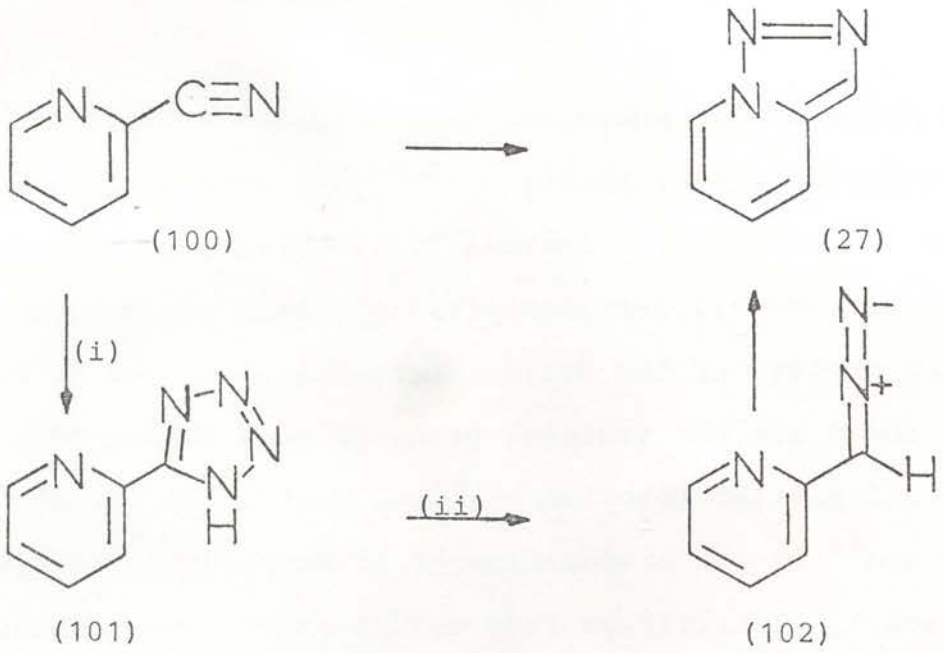
(i) $ArSO_2N_3$

Scheme 20

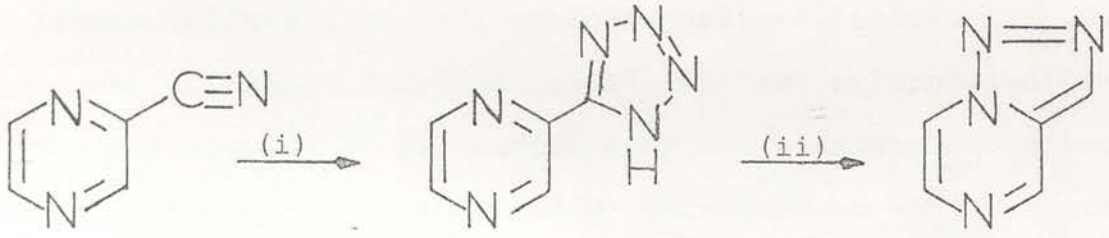
to compounds in which the aryl group is a 2-pyridyl (84) or 2-quinolinyl (87) moiety[17,18,42] the diazo-compounds (85) and (88) are not obtained. Instead 1,2,3-triazolo[5,1-a]pyridines such as (86) and 1,2,3-triazolo[1,5-a]quinolines such as (89), derived from capture of the diazo-intermediates by the heterocyclic nitrogen are the isolated products (see Scheme 19).

A similar reaction has been used by Abramovitch and Takaya[43] in the preparation of triazole-unsubstituted bridgehead fused 1,2,3-triazoles from methyl-substituted benzopyridines (Scheme 20). Although no base was employed tosylazide reacted with 2-methylquinoline (90) to give 1,2,3-triazolo[1,5-a]quinoline (91). This reaction is thought to proceed through the betaine (92). 1-Methylisoquinoline (93) is transformed into 1,2,3-triazolo[1,5-a]isoquinoline (94) in a similar manner but 3-methylisoquinoline (95) failed to react under the same conditions probably due to a reluctance to disrupt the aromaticity of the benzene ring in the linear triazoloisoquinoline (96).

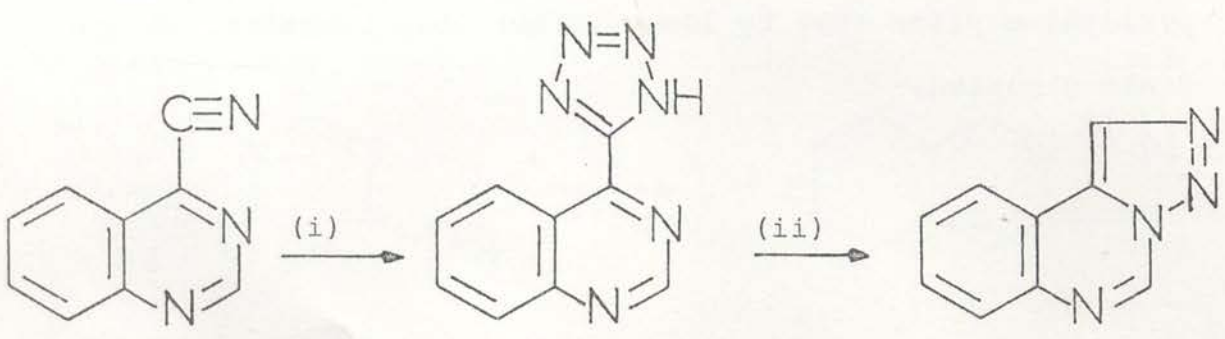
An indication of the greater acidity of a methyl group α to the nitrogen atom in a quinoline nucleus than that on a monocyclic pyridine is demonstrated (Scheme 21) by the fact that 2-methylpyridine (97) when reacted with tosyl azide does not give the triazolopyridine (98) but produces instead the pyridinium ylide (99) by loss, rather than transfer, of the diazo-grouping.



(100) (27) (101) (102)



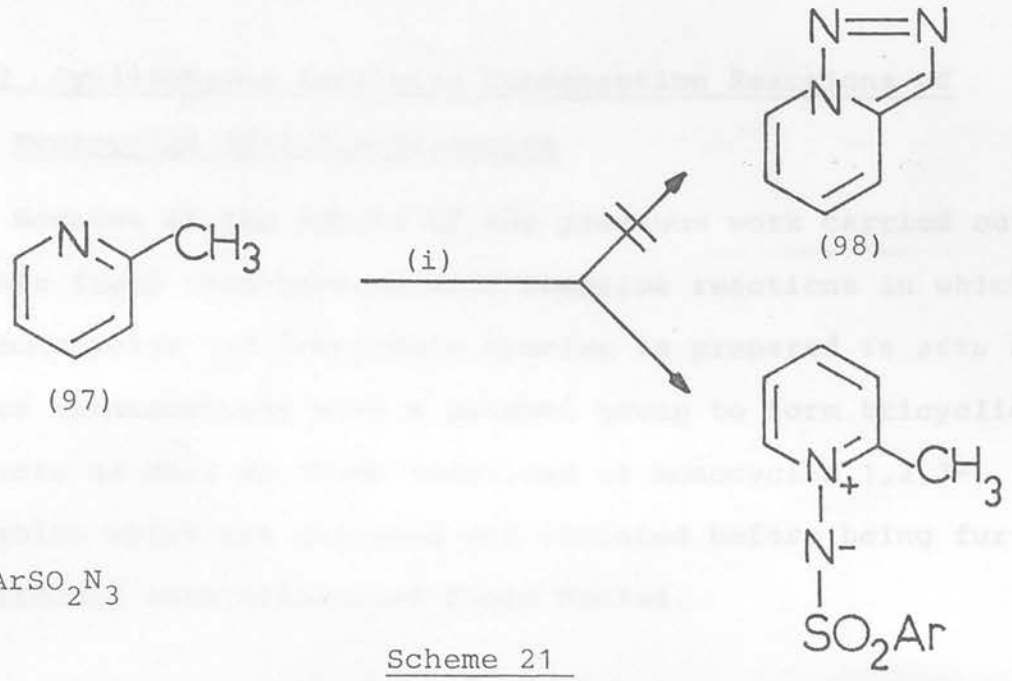
(103) (104) (51)



(105) (106) (107)

(i) HN_3
(ii) heat

Scheme 22



(i) $ArSO_2N_3$

Scheme 21

(e) Generation of the diazo-species by thermal decomposition of tetrazoles

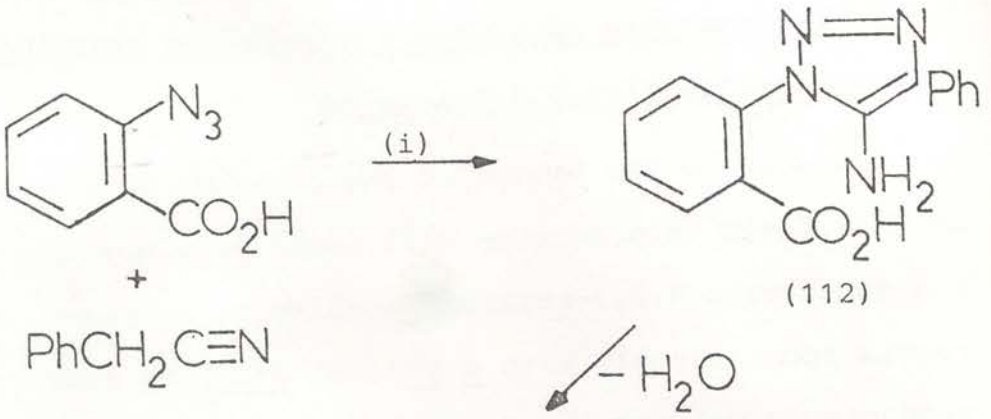
A unique method for the generation of diazo-compounds via the intermediacy of a tetrazole ring has recently been reported by Wentrup.[44] An example of such a synthesis (Scheme 22) is the conversion of 2-cyanopyridine (100) into 2-(1H-tetrazol-5-yl)-pyridine (101) by the action of hydrazoic acid. Subsequent thermal elimination of nitrogen from the latter afforded the diazo-compound (102) and thence the 1,2,3-triazolo[1,5-a]-pyridine (27). The generality of this route to bridgehead-fused 1,2,3-triazole compounds was established by similar transformation of 2-cyanopyrazine (103) and 4-cyanoquinazoline (105) into 1,2,3-triazolo[1,5-a]pyrazine (51) and 1,2,3-triazolo-[1,5-c]quinazoline (107) by way of the tetrazolyl intermediates (104) and (106). The ready availability of the starting materials should make this novel sequence attractive for the preparation of bridgehead-fused 1,2,3-triazoles in future syntheses.

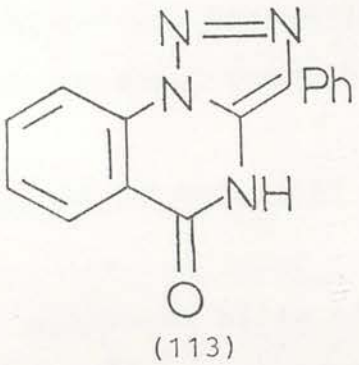
1.3.2 Cyclisations involving Condensation Reactions of Monocyclic 1*H*-1,2,3-Triazoles

Because of the nature of the previous work carried out in this field this section will comprise reactions in which the monocyclic 1,2,3-triazole species is prepared *in situ* and reacts spontaneously with a pendant group to form tricyclic products as well as those reactions of monocyclic 1,2,3-triazoles which are prepared and isolated before being further transformed into bridgehead-fused nuclei.

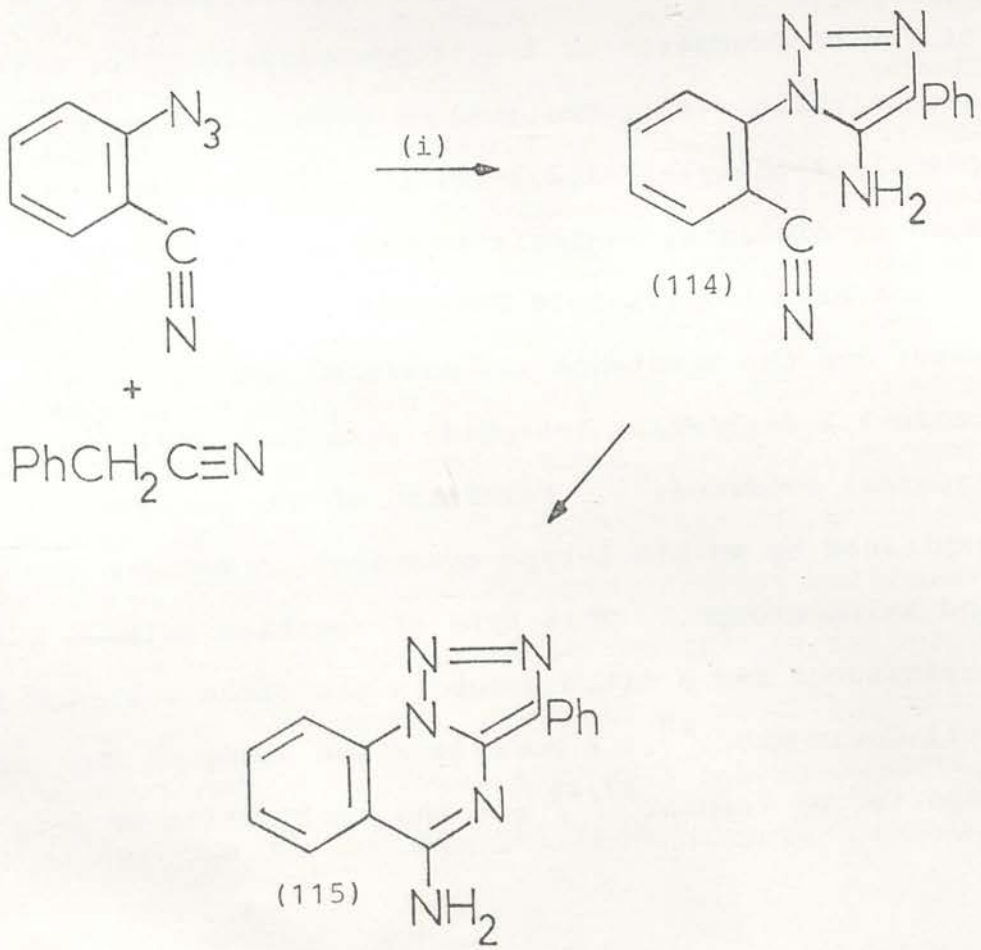
(a) Cyclisation reactions of 1*H*-1,2,3-triazoles formed *in situ*

The advent of the title reactions (Scheme 23) began with the realisation by Lieber *et al*,[45] while studying the Dimroth rearrangement[46] of 5-amino-1*H*-1,2,3-triazoles, that the product of the condensation of 2-nitrophenylazide (108) with phenylacetonitrile (109), designed to give the 5-amino-1-(2-nitrophenyl)-4-phenyl-1*H*-1,2,3-triazole (110), was anomalous. However elemental analysis showed the product to correspond to the expected triazole compound (110) less one molecule of water and the substance was assigned the 1,2,3-triazolo[1,5-a]-benzo-1,2,4-triazine 1-*N*-oxide structure (111) on the basis of chemical evidence.[47] Formation of the product (111) can be explained by an aldol-type condensation between the nitro- and amino-groups. This type of reaction between a benzene substituent and a nitro-group in the ortho position is now well documented.[48] A more detailed study of the reaction was reported by Tennant[47,49] and the cyclisation principle involved

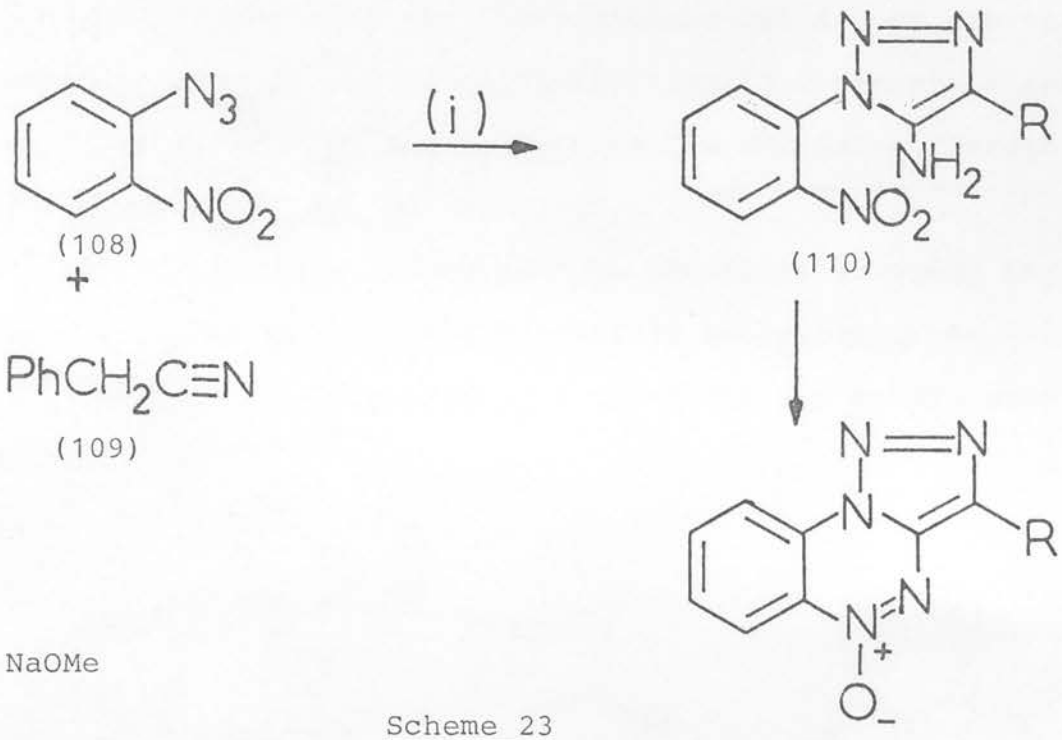

N3
CO2H
+
PhCH2C≡N
(i)
N=N
N
Ph
NH2
CO2H
(112)
- H2O


N=N
N
Ph
NH
O

(113)


N3
C≡N
+
PhCH2C≡N
(i)
N=N
N
Ph
NH2
C≡N
(114)
N=N
N
Ph
N
NH2
(115)

(i) NaOMe

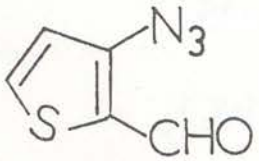


(i) NaOMe

Scheme 23

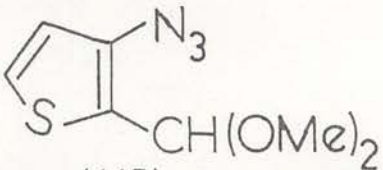
has been extended to provide a synthesis of the 1,2,3-triazolo-[1,5-a]quinazoline ring system (Scheme 24). Thus base-catalysed reaction of 2-azidobenzoic acid with phenylacetonitrile produced the triazoloquinazolone (113)[50] via the intermediate triazole (112) whereas the similar reaction of 2-azidobenzonitrile gave the aminotriazoloquinazoline (115)[51] through cyclisation of the initially formed triazole (114).

The synthetic concept of allowing ortho-substituted azides to react with an activated acetonitrile to give an amino-triazole which due to the close proximity of the ortho-substituent reacts further thereby leading to a bridgehead-fused 1,2,3-triazole system has been further exploited (Scheme 25). 3-Azido-2-formylthiophene (116) as its dimethyl acetal (117) has been treated with activated acetonitriles[52] to give, via the intermediate aminotriazoles (118), the corresponding 1,2,3-triazolo[1,5-a]thieno[3,2-d]pyrimidines (119). In the case



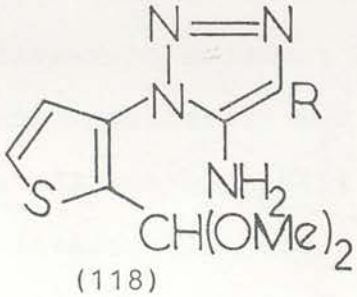
(116)

(i)



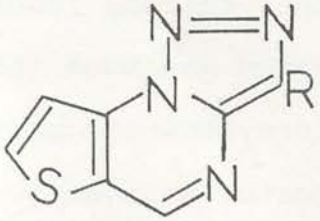
(117)

(ii), (iii)



(118)

(iv)



(119)

(i) MeOH, $HC(OMe)_3$, catalyst

(ii) NaOEt

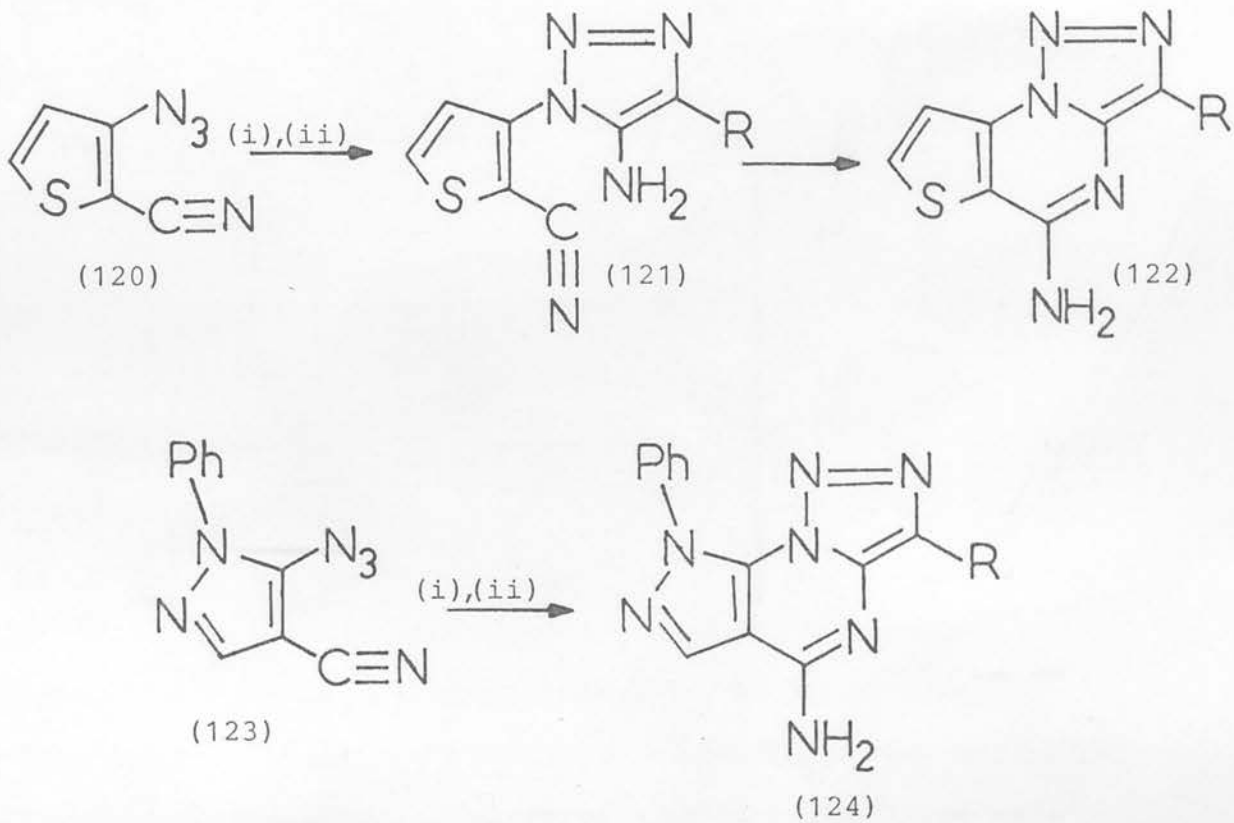
(iii) RCH_2CN

(iv) $AcOH/H_2O$

Scheme 25

of the azido-cyanothiophene (120) (Scheme 26) direct conversion to the 5-amino-1,2,3-triazolo[1,5-a]thieno[3,2-d]pyrimidines (122) results. As in the benzene series the aminotriazole intermediate (121) was not observed.

Khan and Freitas[53] have used an identical strategy to prepare 1,2,3-triazolo[5,1-a]pyrazolo[4,3-e]pyrimidines (124) from 3-azido-4-cyano-1-phenylpyrazole (123) and substituted acetonitriles.

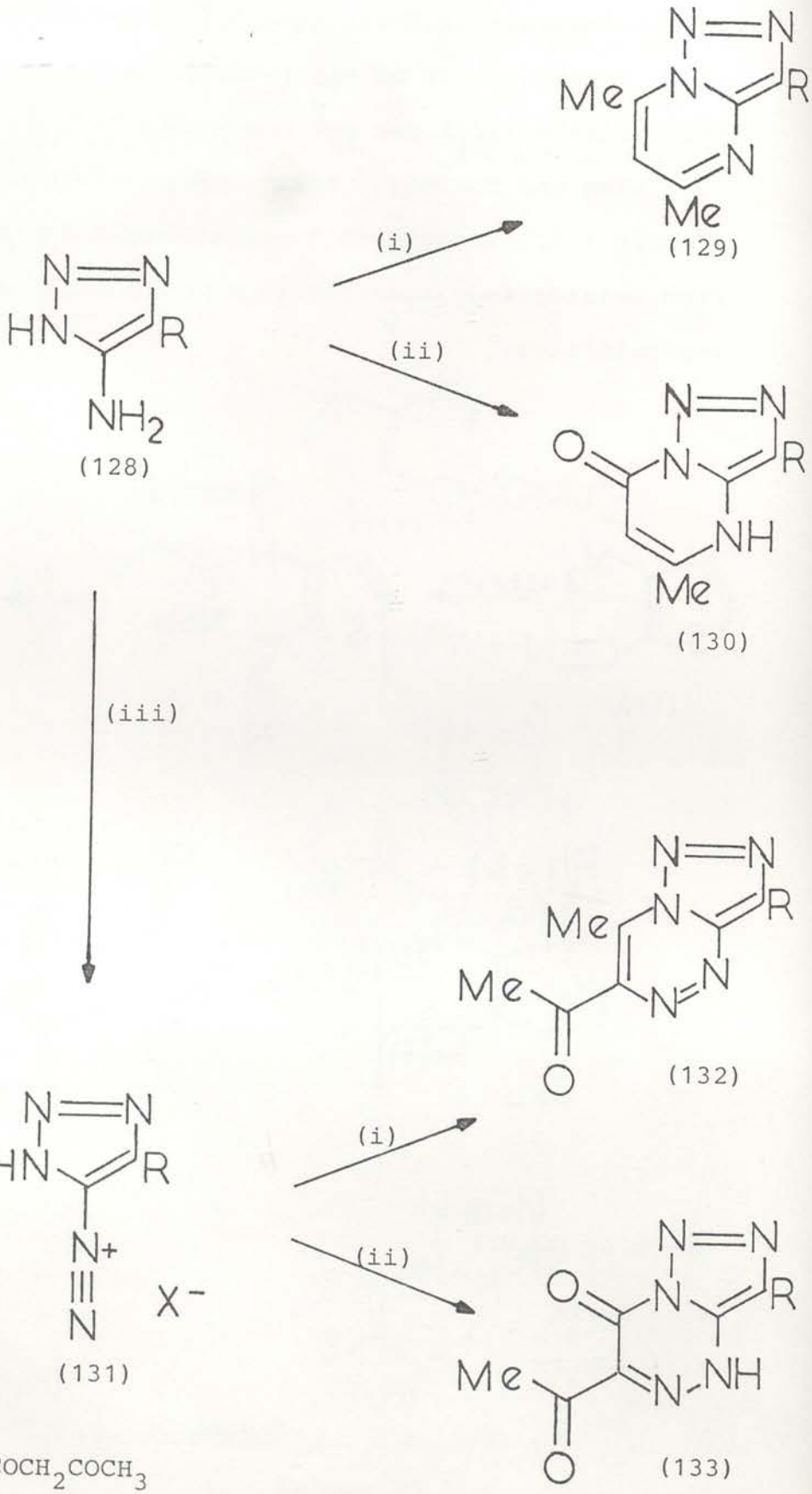


(R=Ph or CO_2Et)

(i) NaOEt

(ii) RCH_2CN

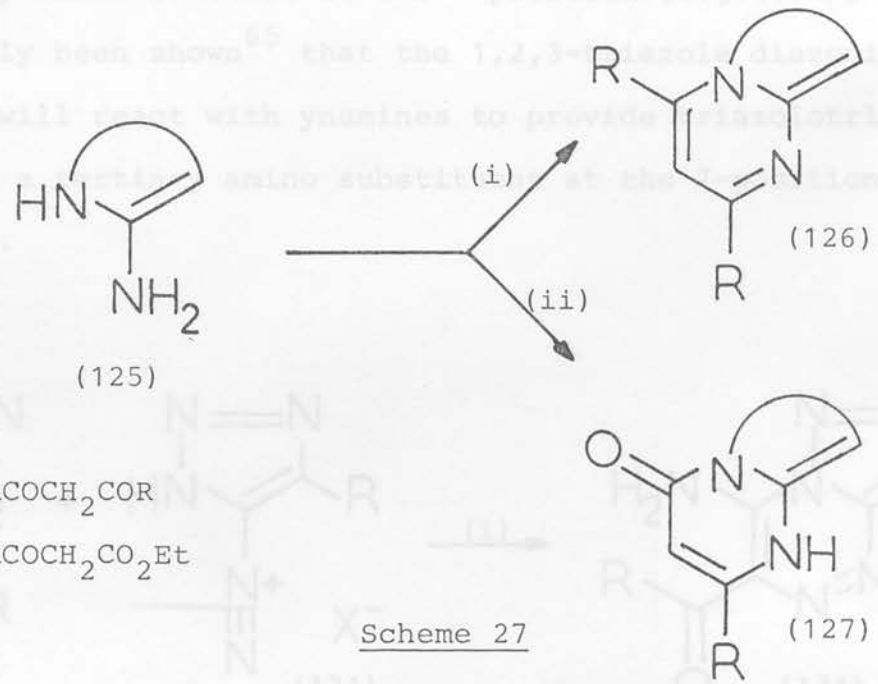
Scheme 26


(128)
(129)
(130)
(131)
(132)
(133)
(i) $CH_3COCH_2COCH_3$
(ii) $CH_3COCH_2CO_2Et$
(iii) dilute $HCl/NaNO_2$

Scheme 28

(b) Cyclisation reactions of isolable 1*H*-1,2,3-triazoles and their derivatives

As early as 1952 Birr[54] described (Scheme 27) the reaction of heterocycles bearing an amino-group α to a ring NH (125) with β-diketones and β-ketoesters to give fused pyrimidines (126) and pyrimidinones (127) respectively although no experimental details were available.[5] Though this became a well



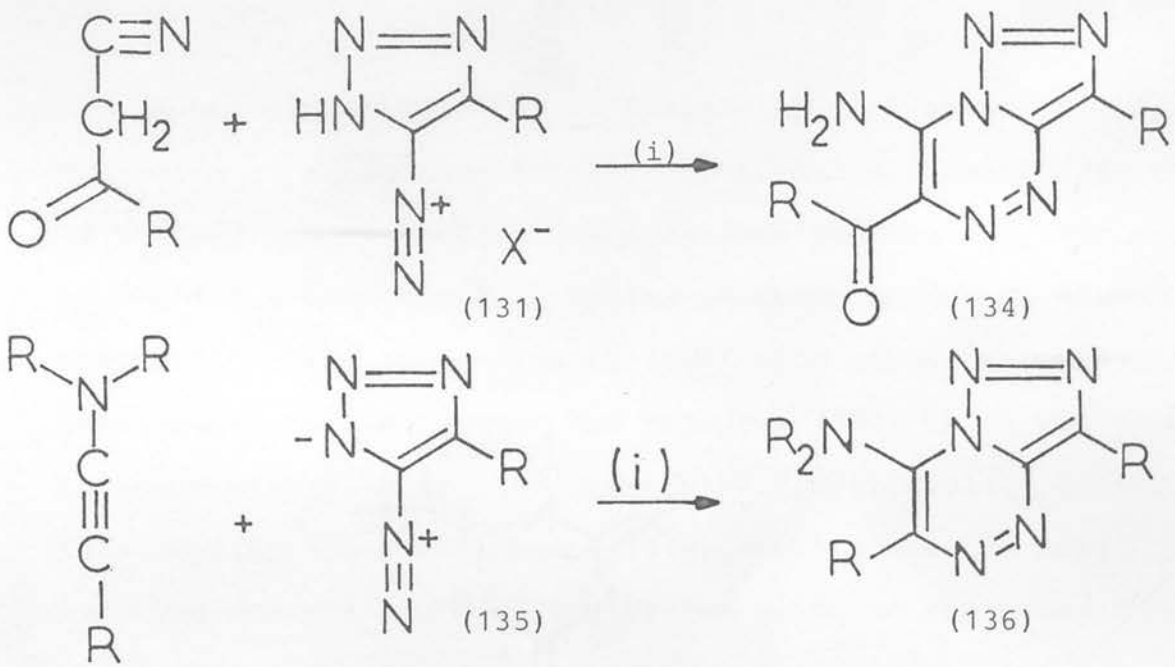
(i) $RCOCH_2COR$

(ii) $RCOCH_2CO_2Et$

Scheme 27

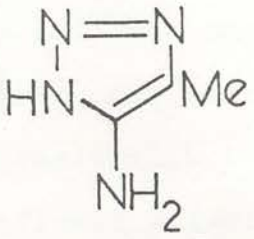
documented process for the preparation of 1,2,4-triazolopyrimidines[55,56] from amino-1,2,4-triazoles it was not until the early 70's that 1,2,3-triazolo[1,5-a]pyrimidines were prepared and studied in detail. Tennant and his co-workers have shown (Scheme 28) that β-dicarbonyl compounds condense smoothly with the readily available[57-60] amino-1,2,3-triazoles (128) to provide 1,2,3-triazolo[1,5-a]pyrimidines. For example[61] reaction with acetylacetone gives 5,7-dimethyl-1,2,3-

triazolo[1,5-a]pyrimidines (129) while ethyl acetoacetate affords[62,63] 5-methyl-1,2,3-triazolo[1,5-a]pyrimidin-7(4H)-ones (130). Furthermore, on diazotisation the aminotriazoles (128) are converted into the diazonium salts (131) and it has been demonstrated[64] that reaction of these salts with β-dicarbonyl compounds gives 1,2,3-triazolo[5,1-c]1,2,4-triazines [e.g.(132) and (133)]. Similar reaction (Scheme 29) with β-ketonitriles results in the formation of triazolotriazines containing a primary amino-function at the 7-position [e.g.(134)] and it has recently been shown[65] that the 1,2,3-triazole diazonium betaines (135) will react with ynamines to provide triazolotriazines having a tertiary amino substituent at the 7-position [e.g. (136)].



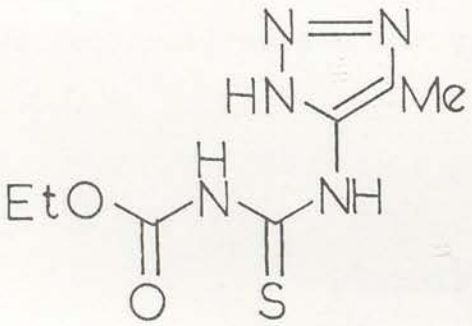
(i) base

Scheme 29



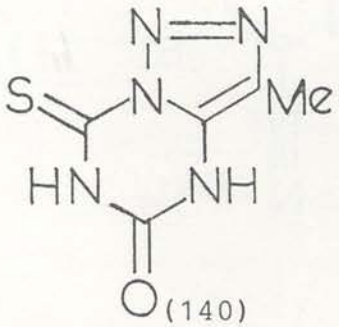
(138)

(i)



(139)

(ii)



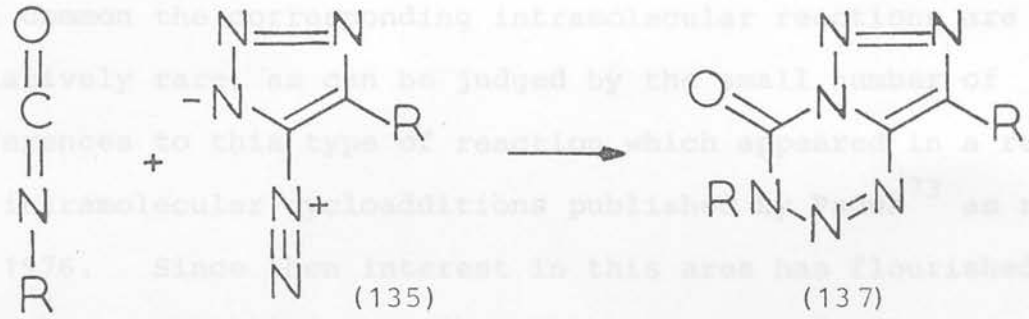
(140)

(i) EtO_2C-NCS

(ii) NaOH

Scheme 31

Another interesting reaction of the diazonium betaines (135) has been reported by Ege *et al*[66] and is outlined in Scheme 30. Under neutral conditions alkyl or aryl isocyanates are reported to react with the diazonium betaines (135) to form the unusual 1,2,3-triazolo[5,1-d]1,2,3,5-tetrazines (137) and this novel system is reported to show unexpected stability.



(135) (137)

Scheme 30

A further example of the reactivity of 5-amino-1*H*-1,2,3-triazoles in bridgehead fused 1,2,3-triazole formation is that of Fox and his co-workers[67] who synthesised the 1,2,3-triazolo-[1,5-a]-1,3,5-triazine ring system as shown in Scheme 31. Treatment of the aminotriazole (138) with ethoxycarbonyl isothiocyanate initially gave the thiourea (139) which was shown to react with base to give 3-methyl-1,2,3-triazolo[1,5-a]-1,3,5-triazin-7(6H)-on-5(4H)-thione (140). This was the only reported example of this ring system prior to the present studies (see Chapter 4).

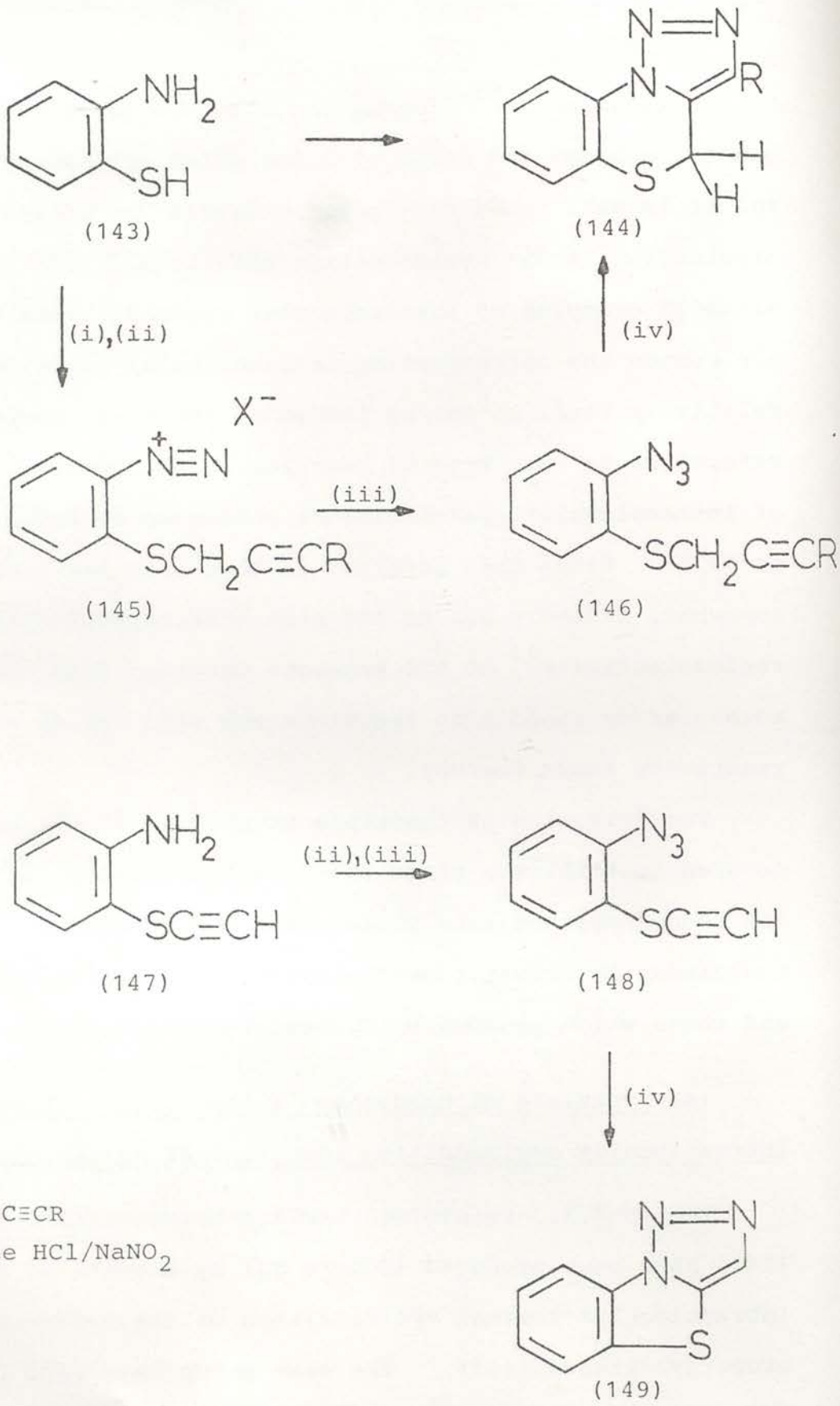
1.3.3 Cyclisations involving Cycloaddition Reactions of Azides

Huisgen *et al*[68-70] were the first to demonstrate the general concept and scope of 1,3-dipolar cycloaddition reactions and it is well known that organic azides can behave as 1,3-dipoles in thermal cycloaddition reactions.[71,72] However, although examples of intermolecular cycloadditions of azides are common the corresponding intramolecular reactions are relatively rare, as can be judged by the small number of references to this type of reaction which appeared in a review of intramolecular cycloadditions published by Padwa[73] as recently as 1976. Since then interest in this area has flourished somewhat, probably due to the high stereospecificity and regioselectivity[74] of the products obtained from these intramolecular cycloaddition reactions and also the diversity of reactivity shown thereby.

The following is therefore an account of the effort devoted to this area since 1976 and for clarity the discussion has been separated into those reactions which give products containing an aromatic bridgehead-fused 1,2,3-triazole structure and those which produce bridgehead-fused 1,2,3-triazolines.

(a) Synthesis of bridgehead fused 1,2,3-triazoles by intramolecular cycloaddition reactions of azides with alkynes

The 4H-1,2,3-triazolo[5,1-c]1,4-benzoxazine derivatives (142) have been prepared (Scheme 32) by Garanti *et al*[75,77] via intramolecular thermal cycloaddition of the *ortho*-azidophenyl-propargyl ethers (141). The same group have also extended this type of synthesis[76] to include the sulphur analogues (144)



(i) $BrCH_2C{\equiv}CR$
(ii) dilute $HCl/NaNO_2$
(iii) NaN_3
(iv) heat

Scheme 33

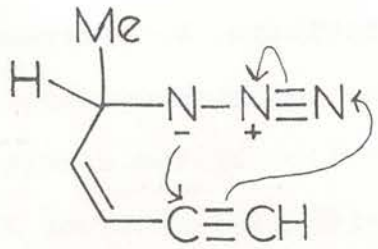
(Scheme 33) by alkylating 2-mercaptoaniline (143) with propargyl bromides followed by diazotisation of the amino-group and substitution of the resulting diazonium salt (145) with azide ion. The azido-alkyne (146) cyclised on heating

(141) (142)

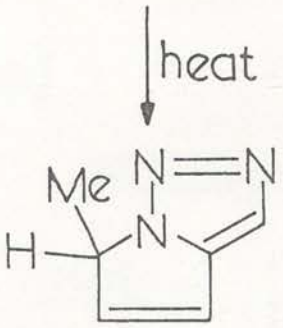
Scheme 32

to give the tricyclic system (144). Moreover it was also found possible to obtain the 1,2,3-triazolo[5,1-b]benzothiazole (149) (Scheme 33) from 2-mercaptoaniline (143) using the same procedure but alkylating the thiol group with bromoacetylene to obtain the amino-alkyne (147). Thus on diazotisation and replacement with sodium azide the alkyne derivative (147) was converted into the azide (148) which cyclised thermally to give the desired bridgehead-fused 1,2,3-triazole. Much of this work has been performed simultaneously[78] by a group of Japanese workers.

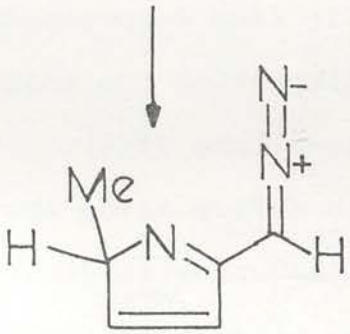
Alkynes have also been shown[79] to react with azides linked intramolecularly through an allyl fragment to produce bridge-head 1,2,3-triazoles fused to a second five-membered ring. For example (Scheme 34) 2-azidohex-3-en-5-yne (150) cyclises thermally to afford 6-methyl-6H-pyrrolo[1,2-c]-1,2,3-triazole (151). Evidently, as the spectroscopic properties of the product are stated[79] to be fully in accord with the structure (151) there is no tendency for the latter to ring-open to the



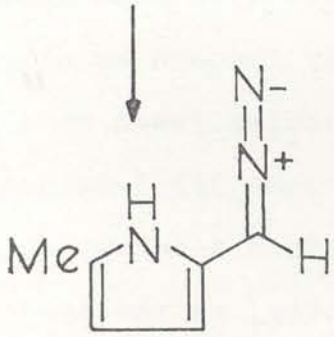
(150)



(151)



(152)



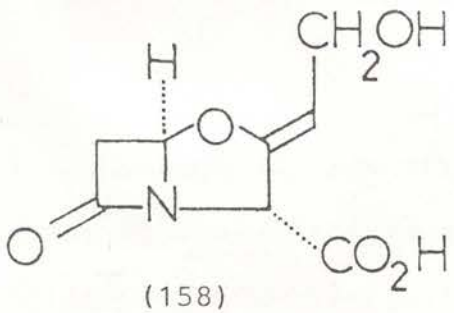
(153)

Scheme 34

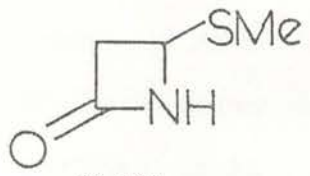
diazo-compound (153) via the open-chain intermediate (152). In contrast, the ring-chain tautomerism of the analogous bridgehead-fused 1,2,3-triazoles containing a six-membered ring, which occurs at elevated temperatures, is well documented[80] and the steric strain imposed by the fused 5:5-system might have been expected to promote similar tautomeric ring-opening in (151). The lack of such rearrangement, at least at room temperature, can however be explained by the reluctance of the bicyclic triazole (151) to lose the aromatic stabilisation consequent on ring-opening to the non-aromatic pyrrole derivative though this could be compensated for by subsequent 1,5-hydrogen shift to give the aromatic diazoalkylpyrrole derivative (153).

While conducting a general investigation of fused benzimidazoles, Hideg and Hankovsky[81] treated (Scheme 35) the chloroalkyl-1H-benzimidazole (154) firstly with sodium azide followed by propargyl bromide and obtained the tetracyclic bridgehead-fused 1,2,3-triazole (155) presumably via the azido-compound (156) and then cyclisation of the alkyne (157).

An example of a bridgehead-fused 1,2,3-triazole which possesses biological activity has been reported by Pearson *et al.*[82] During investigations on the synthesis of analogues of the potent β-lactamase inhibitor 'clavulanic acid' (158) the Beecham workers reasoned that the exocyclic double bond at the 2-position could be fixed at that position by being contained within a heterocyclic ring (i.e. a 1,2,3-triazole ring). Their synthetic strategy (Scheme 36) therefore involved transformation of the readily available 4-thiomethylazetidin-2-one (159) by chlorinolysis and treatment with sodium azide

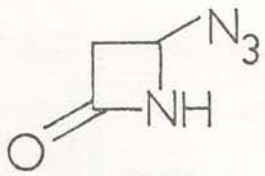


(158)



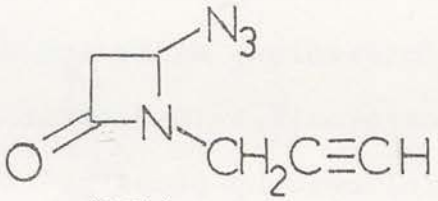
(159)

(i)



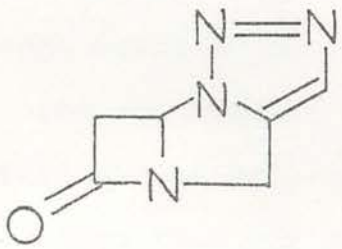
(160)

(ii)

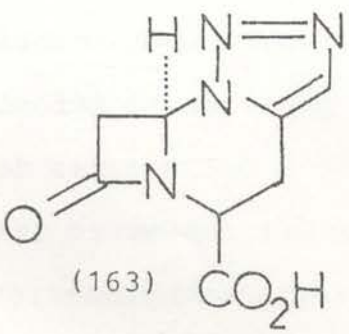


(161)

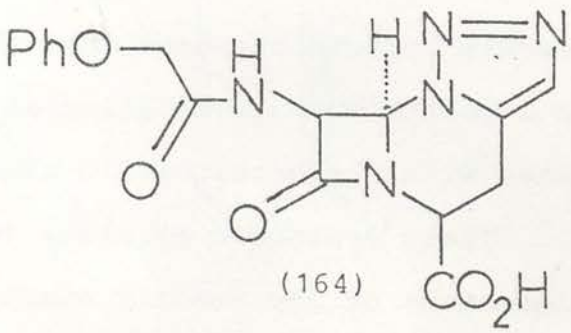
(iii)



(162)



(163)



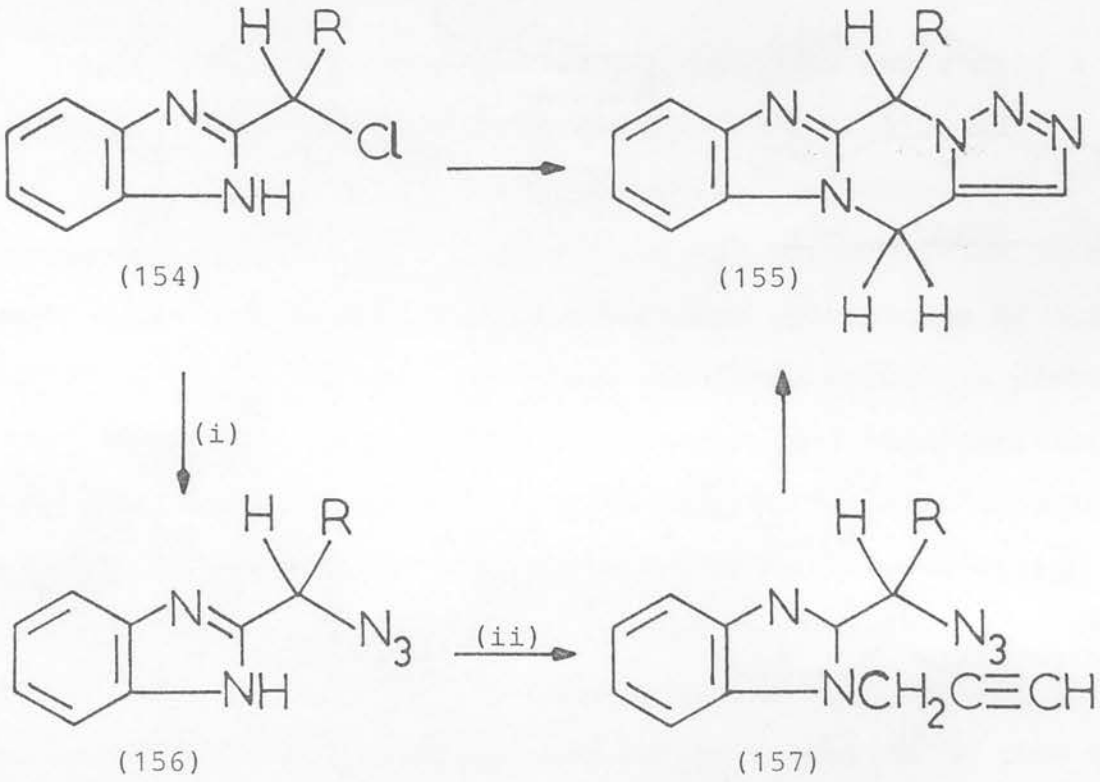
(164)

(i) Cl_2 then NaN_3

(ii) $BrCH_2C{\equiv}CH$

(iii) heat

Scheme 36

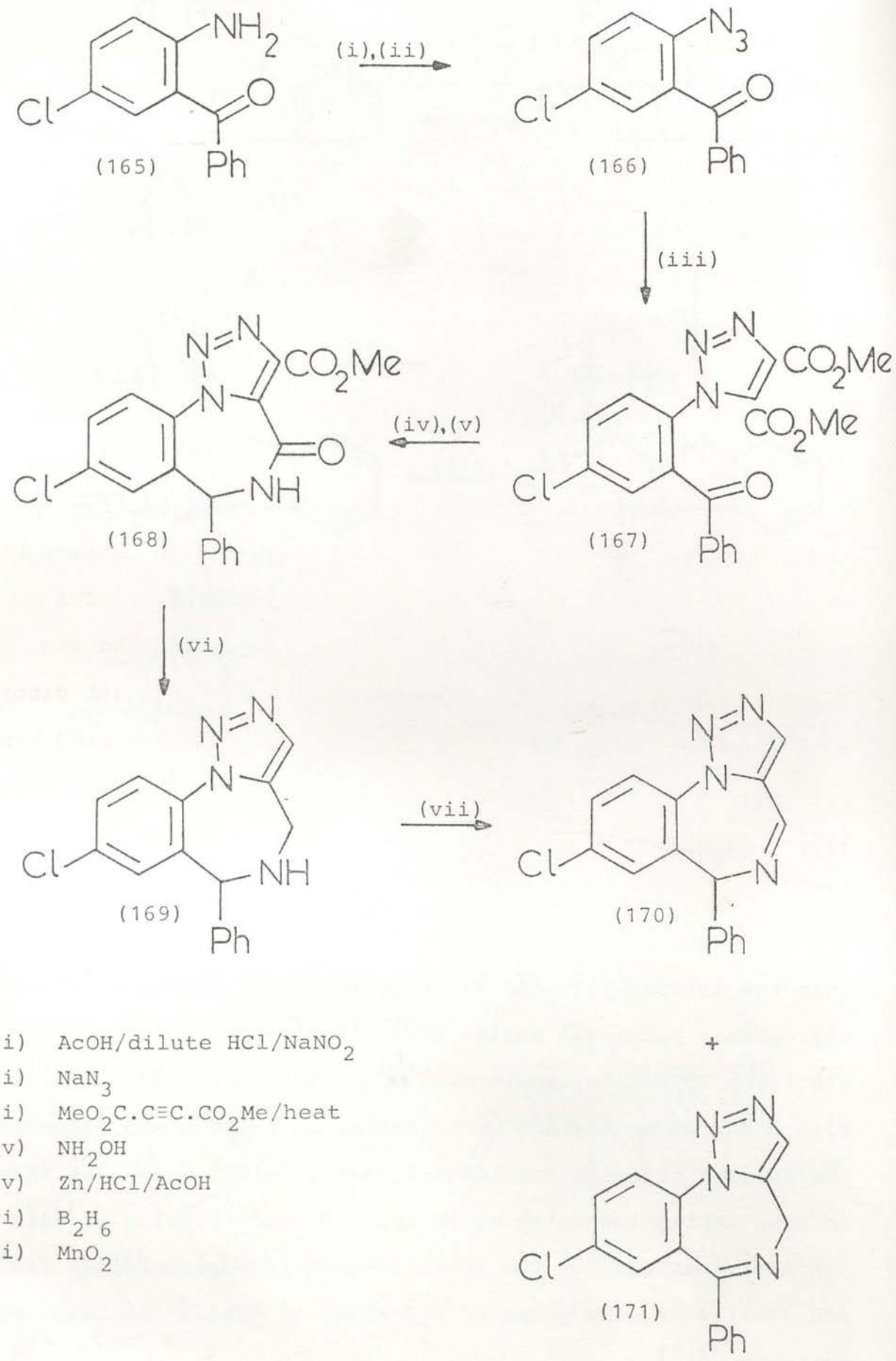


(i) NaN_3

(ii) $BrCH_2C{\equiv}CH$

Scheme 35

into the azidoazetidinone (160), reaction of which, with the appropriate propargyl halide then afforded the azido-alkyne (161) set up for intramolecular cycloaddition. Such cyclisation occurred on heating under reflux in toluene and afforded the desired triazolo-azetidino-imidazole (162) which was found to have anti-β-lactamase activity. By modification of this synthetic methodology the triazolo-azetidino-pyrimidines (163) and (164) were also prepared and shown to exhibit antimicrobial activity.[83,84]

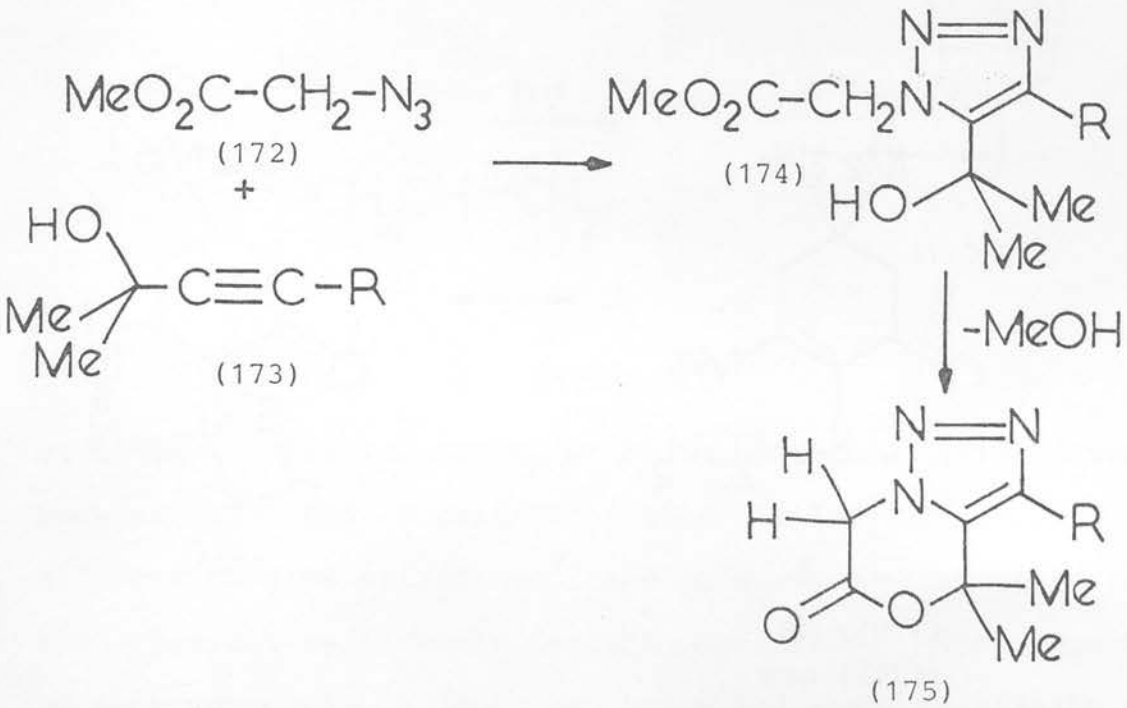


(i) AcOH/dilute HCl/$NaNO_2$
(ii) NaN_3
(iii) $MeO_2C.C{\equiv}C.CO_2Me$/heat
(iv) NH_2OH
(v) Zn/HCl/AcOH
(vi) B_2H_6
(vii) MnO_2

Scheme 37

Potentially biologically active compounds containing a bridgehead-fused 1,2,3-triazole nucleus have also been reported by Coffen *et al*[85] amongst others[86] although the synthesis involved initial intermolecular cycloaddition of an azide to an alkyne followed by subsequent cyclisation of the resulting 1,2,3-triazole to afford the fused structure (Scheme 37). Thus, the readily available 2-benzoyl-4-chloroaniline (165) was converted by diazotisation and azido-dediazoniation into the azido-compound (166) which underwent cycloaddition to dimethyl acetylenedicarboxylate to give the triazole derivative (167). Conversion into the oxime followed by reduction to the amine resulted in spontaneous lactam formation to give the 6H-1,2,3-triazolo[1,5-a]1,4-benzodiazepinone (168). The unwanted ester group at the 3-position was removed and the carbonyl moiety in the seven-membered ring reduced with diborane to give the 4,5-dihydro derivative (169). This compound was oxidised with activated manganese dioxide thereby giving rise to the triazolobenzodiazepine derivatives (170) and (171). No data on the biological properties of these compounds was reported but an earlier patent, which seems to cover these derivatives, claims tranquilizing and anticonvulsive properties.[86]

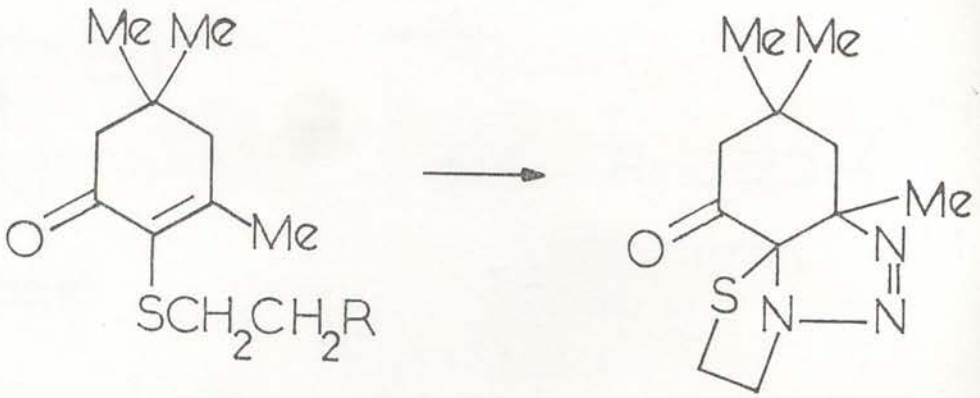
The reaction sequence of intermolecular azide to alkyne cycloaddition followed by intramolecular cyclisation has also been used to prepare bridgehead-fused 1,2,3-triazolo-1,4-oxazines (Scheme 38). For instance, azidoacetates such as (172) have been shown[87] to react with α-hydroxyalkynes (173) to give 4H-1,2,3-triazolo[5,1-c]1,4-oxazin-6(7H)-ones (175) by spontaneous cyclisation of the substituted triazoles (174).



Scheme 38

(b) Synthesis of bridgehead-fused 1,2,3-triazolines by intramolecular cycloaddition reactions of azides and alkenes

While studying the related intramolecular azide-alkyne cycloaddition reactions (see before) Garanti *et al*[75] also showed (Scheme 39) that the analogous *ortho*-azidophenylallyl ether (176) can be cyclised photochemically to give the bridgehead-fused triazoline derivative (177) and have, as well as Smith *et al*[87], studied the reactivity of these compounds. Interest in this type of bridgehead-fused triazoline is due in part to their ease of formation, the high stereospecificity for the *cis* mode of cycloaddition[88-91] and the regiospecificity of product formation (which is not always found in the intermolecular cycloadditions of azides to olefins but which is imposed by the steric constraints of the intramolecular



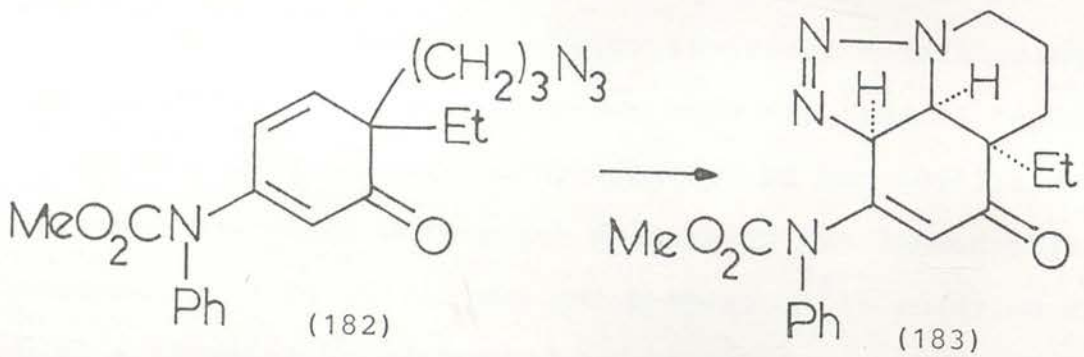
R

(178); OH

(179); OMs

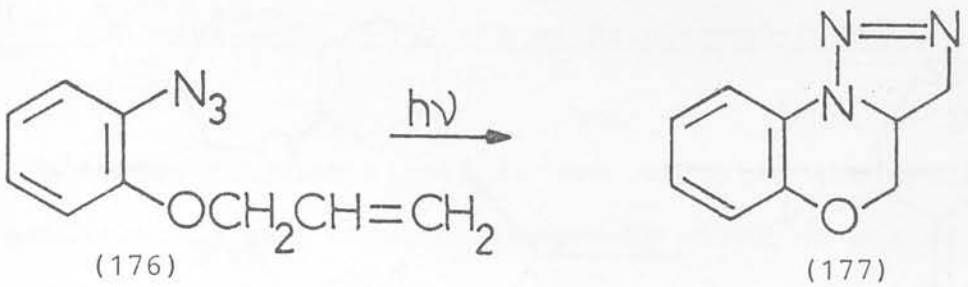
(180); N_3

(181)



(182) (183)

Scheme 40



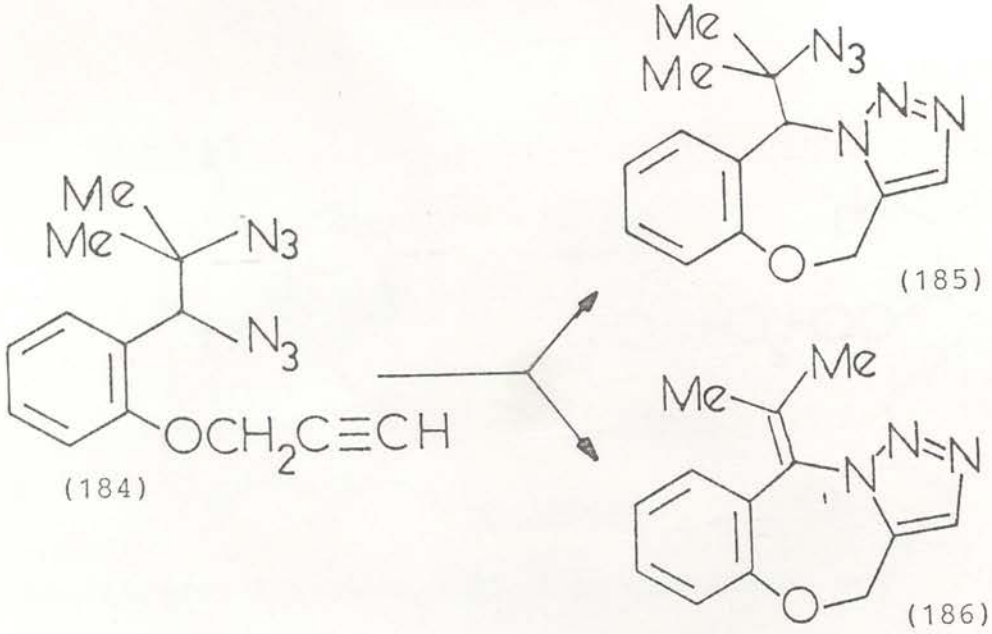
(176) (177)

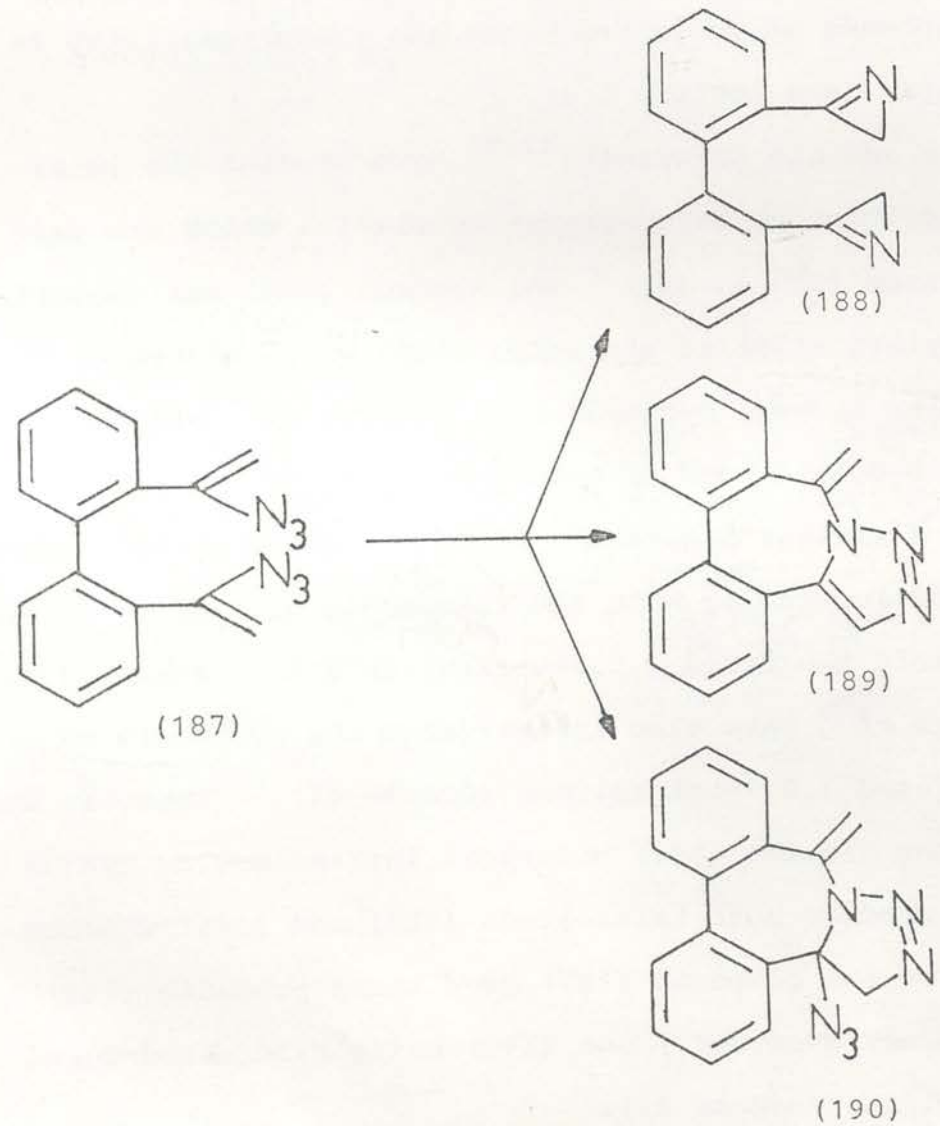
Scheme 39

reaction). The reactivity of bridgehead-fused triazolines such as (177) and in particular their ability to extrude nitrogen to give aziridines[92] and products derived therefrom also contributes to their current popularity. The preparation of such compounds is described below and their reactivity is outlined later (see Section 1.4).

Schultz and his co-workers[93,94] have studied the intramolecular addition of azido-groups to olefins which are part of an enone system (Scheme 40). The alcohol (178) was converted via the mesylate (179) to the azide (180) which underwent intramolecular thermal cycloaddition between the azido-group and the enone double bond to give the tricyclic triazoline (181). In a similar sequence[94] the azido-group in the compound (182) reacted internally with the γ,δ-double bond of the dienone system to yield the fused 1,2,3-triazoline (183) (Scheme 40).

Padwa *et al*[95] have also investigated the synthesis of bridgehead-fused 1,2,3-triazolines (Scheme 41). Thus, it was found that the diazide (184) underwent intramolecular cycloaddition to produce both triazolines (185) and (186) whereas thermolysis of the compound (187) gave three products (188)-(190), the minor ones (189) and (190) being bridgehead-fused 1,2,3-triazolines (Scheme 41).

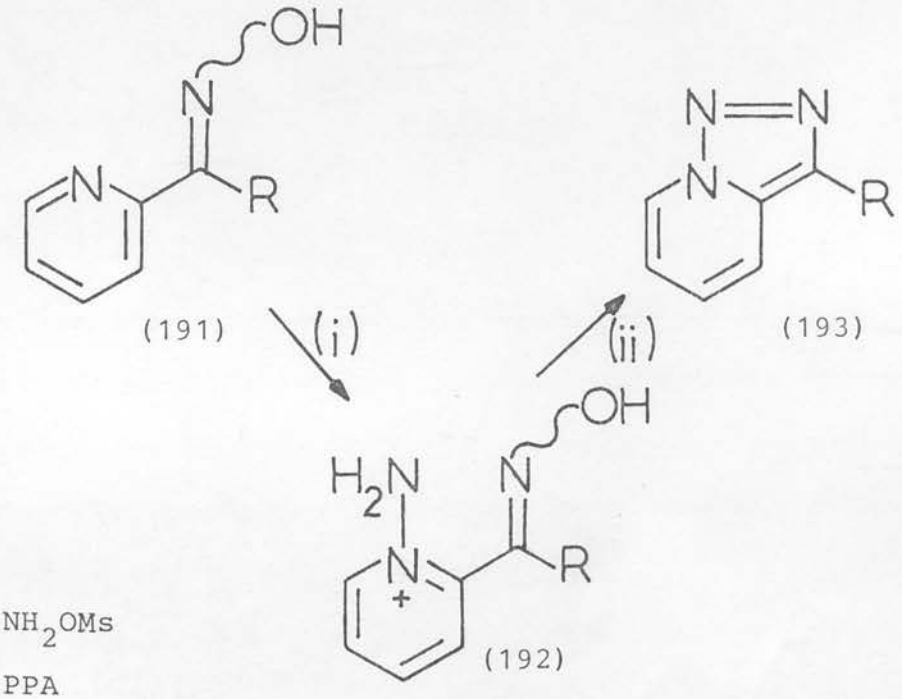




Scheme 41

1.3.4 Miscellaneous Syntheses of Bridgehead-fused 1,2,3-Triazoles

A number of communications have reported the synthesis of bridgehead-fused triazole compounds which do not fit into any of the previous categories.[96-98] For example (Scheme 42) it has been shown[96] that the oxime (191) can be converted into the triazolopyridine (193) by the action of hydroxylamine-O-sulphonic acid. The initially-formed *N*-aminopyridinium species (192) was cyclised in polyphosphoric acid to give the desired 1,2,3-triazolopyridine (193) by elimination of water, however it is reported that only the E-isomer of the oxime (191) will react in this way, the corresponding Z-isomer affording only intractable mixtures.

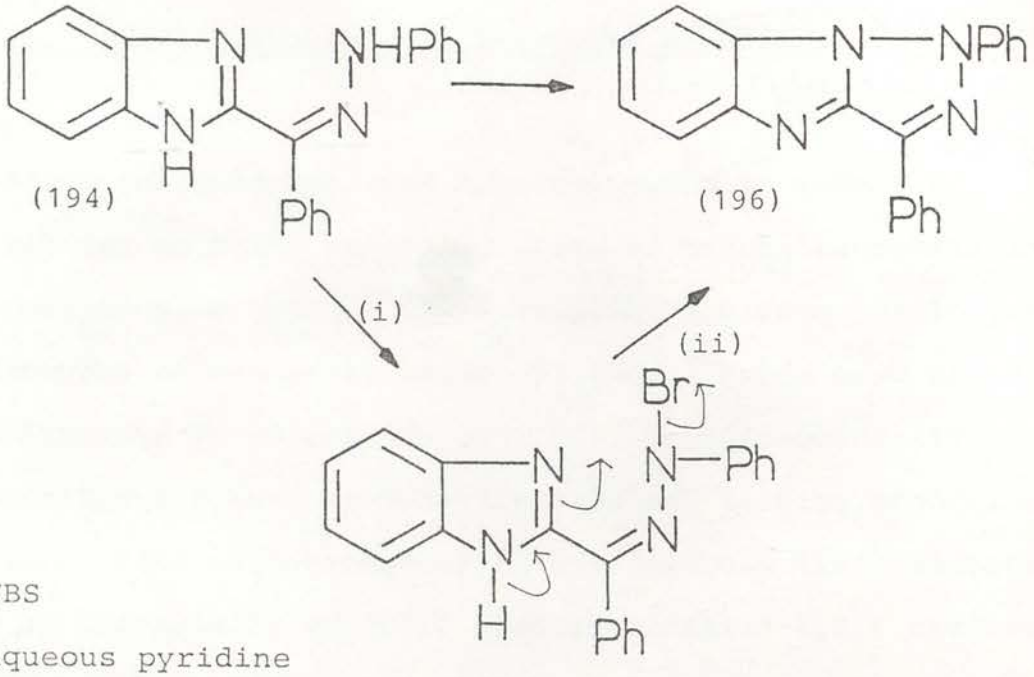


(i) NH_2OMs

(ii) PPA

Scheme 42

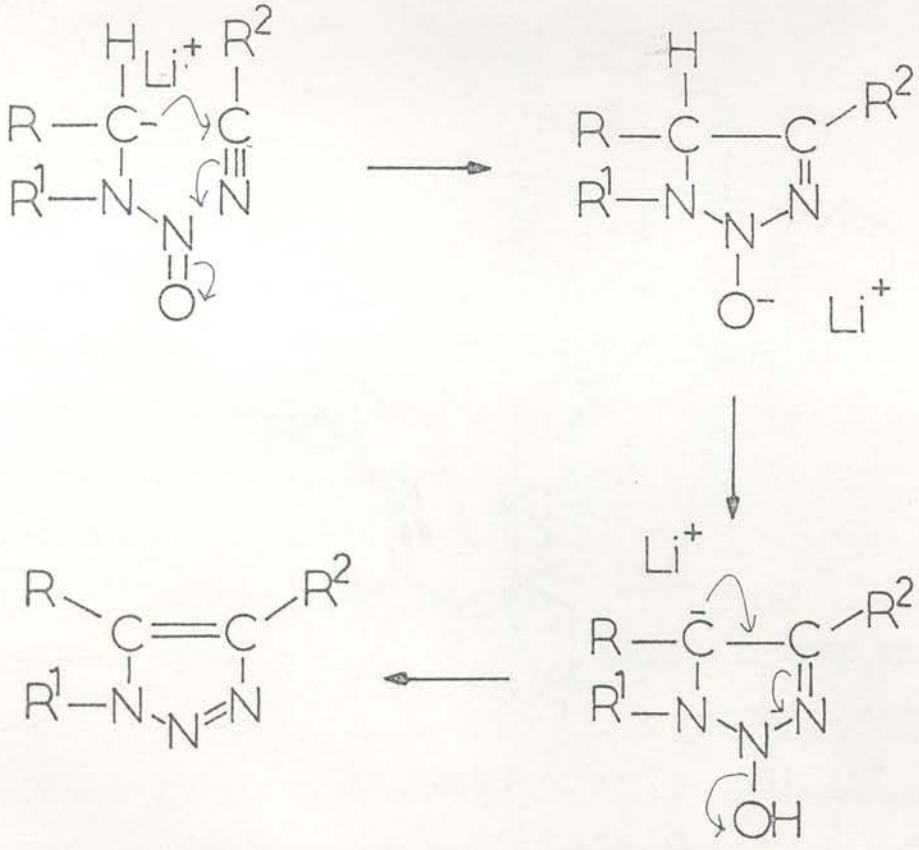
Gelleri and Messmer[97] have reported (Scheme 43) that



(i) NBS

(ii) aqueous pyridine

Scheme 43



Scheme 44

bromination of the phenylhydrazone (194) produces the 1H-1,2,3-triazolo[5,1-a]benzimidazole (196) presumably by way of the bromo-compound (195).

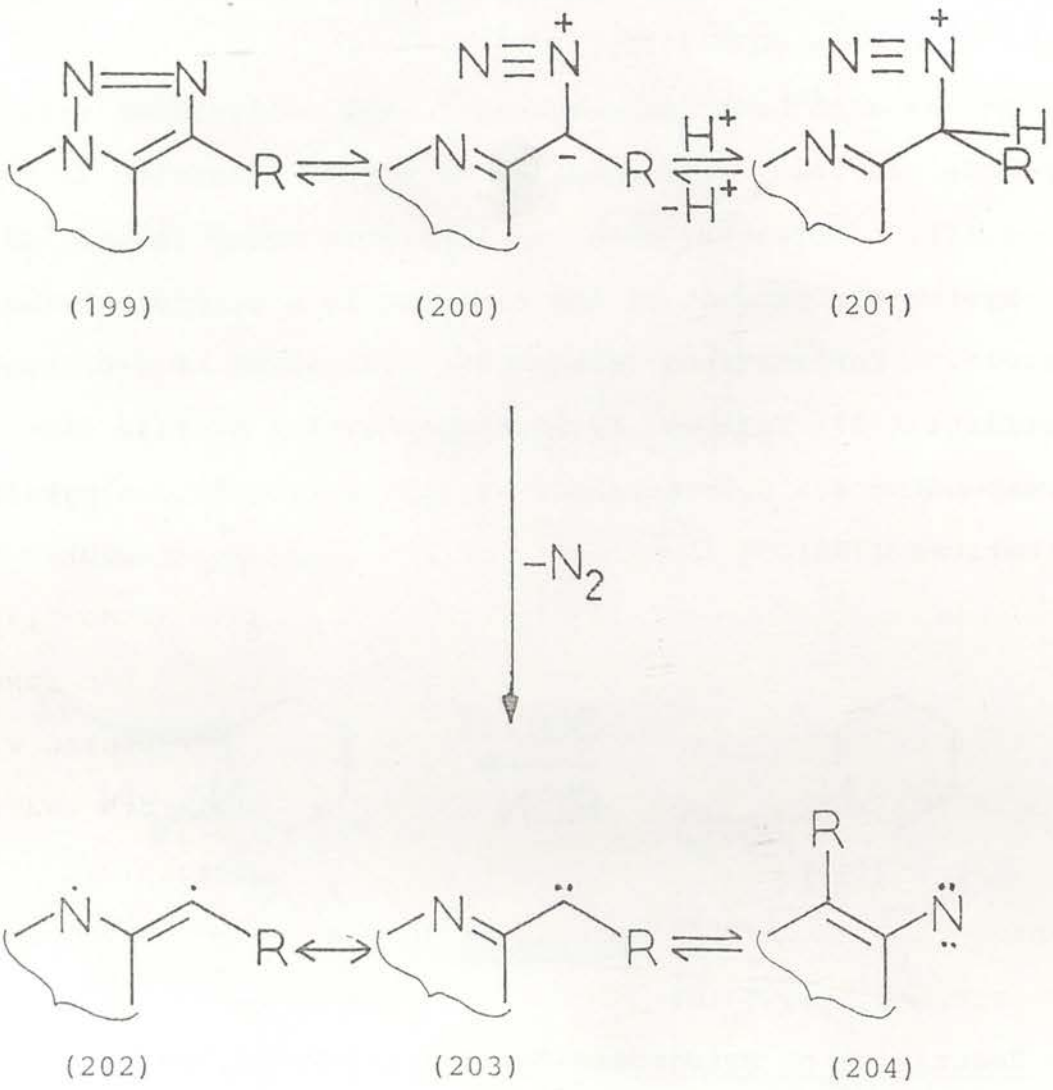
It has also been demonstrated[98] that α-lithiated *N*-nitroso compounds can react with nitriles to afford triazoles (e.g. Scheme 44). Moreover, when the *N*-nitroso group is part of a ring-system the product of the reaction is a bridgehead-fused triazole. For instance (Scheme 45) lithiation of *N*-nitroso-piperidine (197) followed by treatment with a nitrile gave the corresponding 4,5,6,7-tetrahydro-1,2,3-triazolo[1,5-a]pyridine derivatives (198).

(197) (198)

Scheme 45

1.4 Reactivity of Bridgehead-fused 1,2,3-Triazoles

Molecules which contain a bridgehead-fused 1,2,3-triazole nucleus [Scheme 46; (199)] are of considerable interest as precursors for the generation and study of a variety of reactive heterocyclic species in that they often exhibit reactivity akin to the open chain diazoalkyl tautomers (200). In acidic media products are formed which are derived from the diazonium cations (201)[47,49-53,99,100] whereas in neutral media homolytic ring cleavage can occur to afford products derived from intermediate carbenes (203) or, by rearrangement, nitrenes (204).[101-105] Recently it has been shown that the diradical (202) can



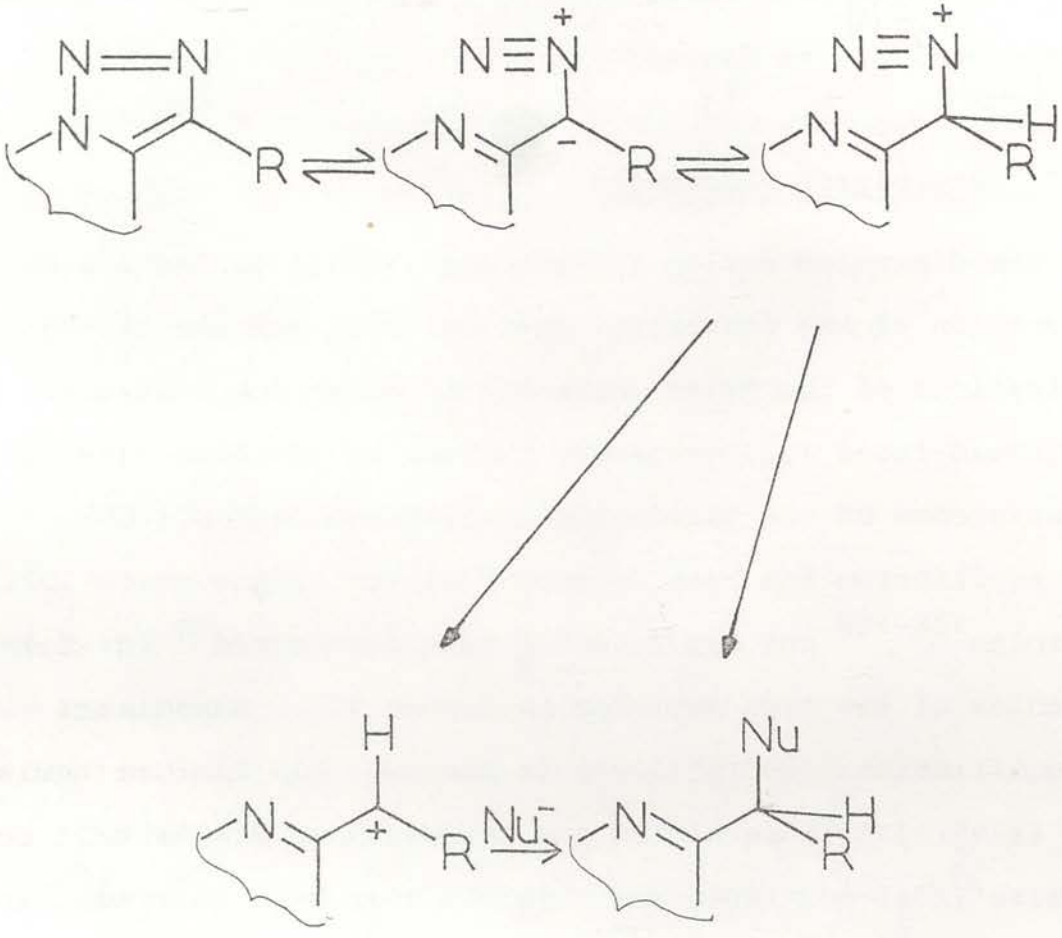
Scheme 46

also be generated and products derived from this species have been observed.[93,94] The reactivity of bridgehead-fused 1,2,3-triazoles attributable to each of these types of intermediate will now be discussed.

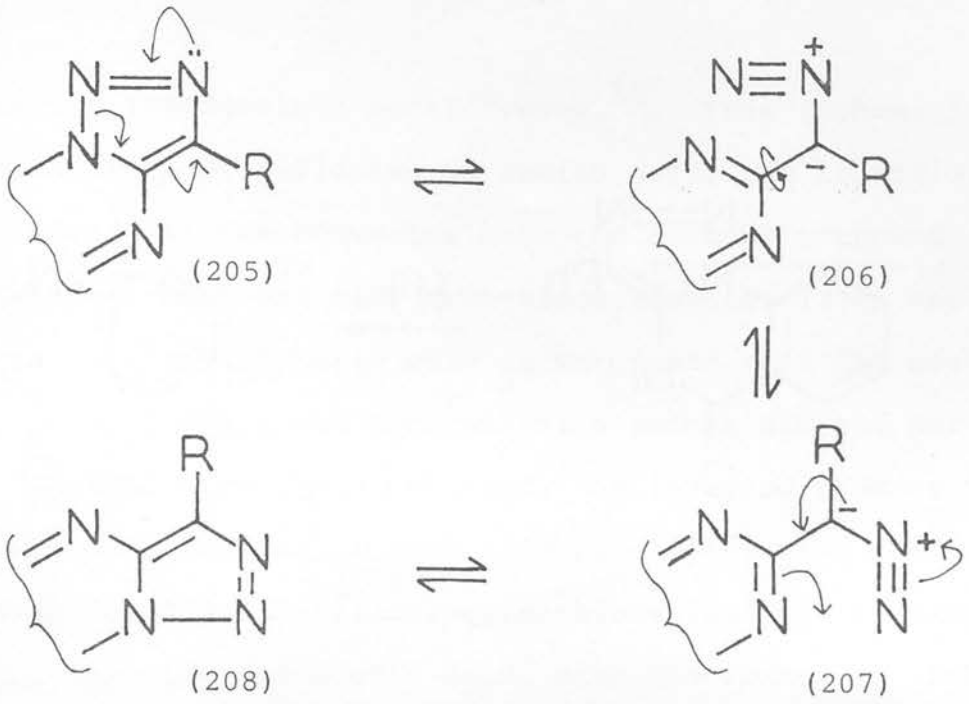
1.4.1 Heterolytic reactivity

The diazonium cation [Scheme 46; (201)] is derived by protonation of the diazoalkyl species (200) and one of the implications of the diazo-character of molecules containing a bridgehead-fused 1,2,3-triazole nucleus of the type (199) is the existence of the tautomeric equilibrium (199)$\rightleftharpoons$(200). This equilibrium has been demonstrated for simple amino-1,2,3-triazoles[106-108] and has recently been documented[80] for fused triazoles of the type depicted in Scheme 47. Associated with the equilibrium [(205)$\rightleftharpoons$(206)] is the possible Dimroth rearrangement [(205)$\rightarrow$(208)] involving the intermediate diazoalkyl rotamers (206) and (207) and this has also been observed for unsymmetrical bridgehead-fused 1,2,3-triazoles.[50,61,62]

Under acidic conditions bridgehead-fused 1,2,3-triazoles are ring-cleaved to provide substituted heterocycles[48,49,52,61,62,100,109] and it has been proposed[48] that the diazonium cations [Scheme 46; (201)] are intermediates in this reaction. Subsequent direct displacement of the diazonium group by a nucleophile or initial loss of the diazonium group followed by reaction of the resulting carbonium ion with solvent would lead in either case to products in which a 1:1 addition of an acidic reagent has occurred with loss of nitrogen (see Scheme 48). In this respect the finding of Regitz[99] that treatment

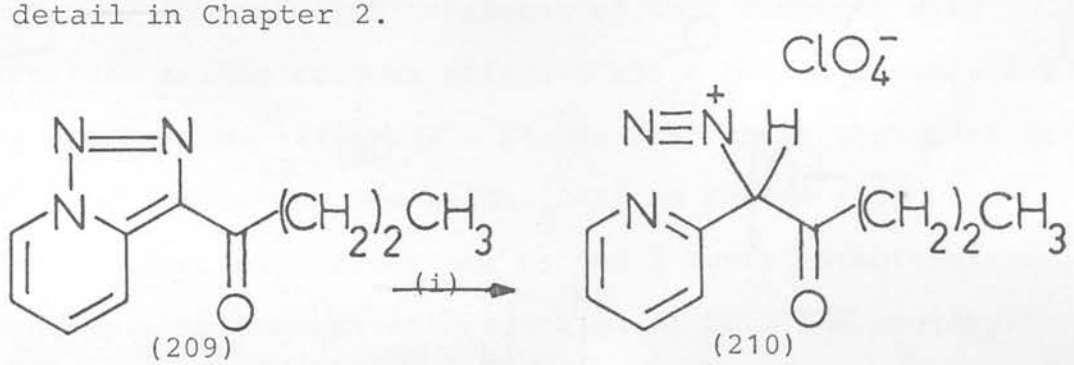


Scheme 48



Scheme 47

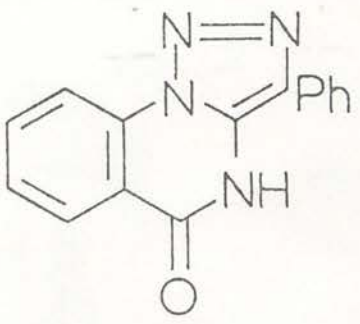
of the triazolopyridine derivative [Scheme 49; (209)] with perchloric acid produced the stable diazonium perchlorate (210) is evidence for this mechanism but does not distinguish between the two possible pathways that the diazonium salt could take. The mechanism of such reactions will be discussed in greater detail in Chapter 2.



(i) $HClO_4$

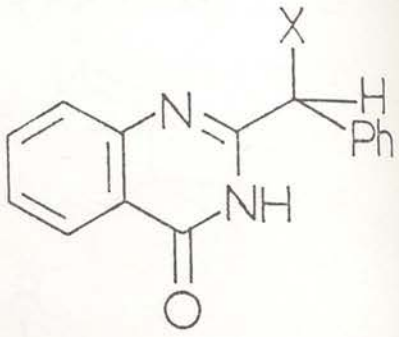
Scheme 49

Although acid promoted cleavage of bridgehead-fused 1,2,3-triazoles had been previously reported by Boyer and Wolford[30], Tennant and his co-workers were the first to exploit the concept of triazole scission to provide synthetic routes



(211)

(i)



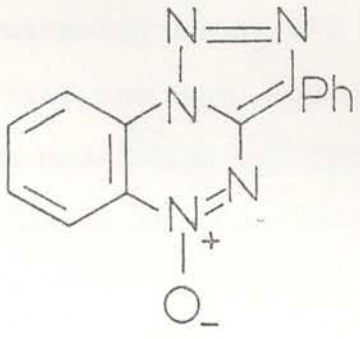
(212)

X

a; OAc

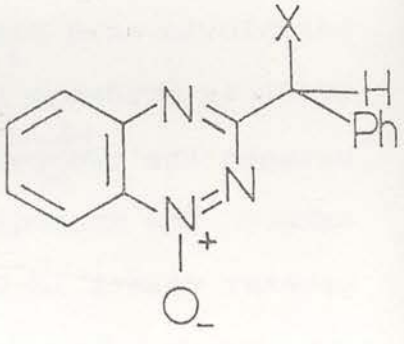
b; OH

c; Cl



(213)

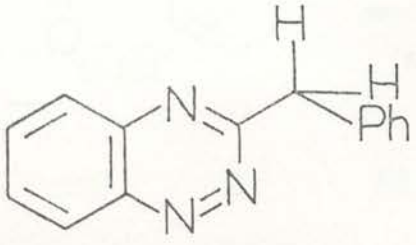
(i)



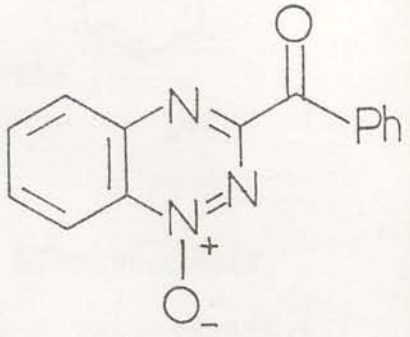
(214)

(ii)

(iii)



(215)



(216)

(i) a; H_2SO_4/H_2O

b; AcOH

c; AcCl/AcOH

(ii) NaS_2O_4

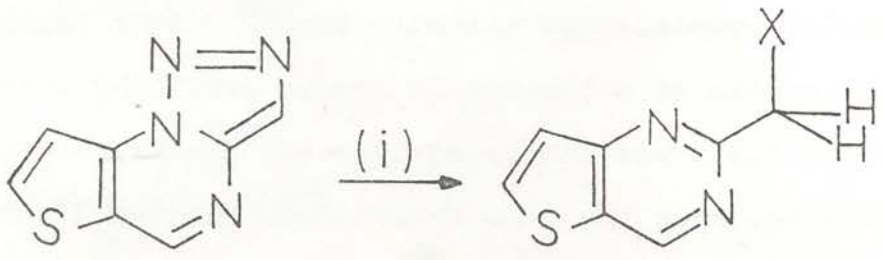
(iii) CrO_3/AcOH

Scheme 50

to otherwise inaccessible heterocycles.[50] Thus (Scheme 50) under conditions of refluxing in acetic acid, the triazoloquinazolone (211) was converted into the acetoxy compound (212a) whereas when the same triazoloquinazolone (211) was heated in aqueous sulphuric acid it was found that the weakly nucleophilic sulphate and hydrosulphate anions did not participate. Instead hydrolysis occurred, the isolated product from this reaction being the alcohol (212b). By heating the bridgehead-fused 1,2,3-triazoloquinazolone (211) in a mixture of acetyl chloride and acetic acid, with the former in excess, it was shown that the chloro-compound (212c) was obtained in good yield. This result is presumably due to the *in situ* metathesis of acetyl chloride and acetic acid to give acetic anhydride and hydrogen chloride, the species which promotes the triazole scission in this case.

Another paper[49] details the analogous scission reactions (Scheme 50) of the triazolobenzotriazine 1-*N*-oxide (213) and it was reported that similar treatment of this compound with the appropriate acidic reagent afforded the expected benzotriazine 1-*N*-oxide derivatives (214a-c). It was also shown that heating the triazolobenzotriazine 1-*N*-oxide (213) in acetic acid with sodium dithionite caused reduction to the 3-benzylbenzotriazine (215) presumably by concomitant reduction of both the acetoxybenzyl side-chain and the *N*-oxide function. Conversely heating in acetic acid in the presence of chromium trioxide gave an oxidation product identified as the 3-benzoylbenzotriazine 1-*N*-oxide (216).

The triazolo[1,5-a]pyrazine (51) and the triazolo[1,5-b]-pyridazine (57) ring systems (Scheme 51) have also been



(219)

(220)

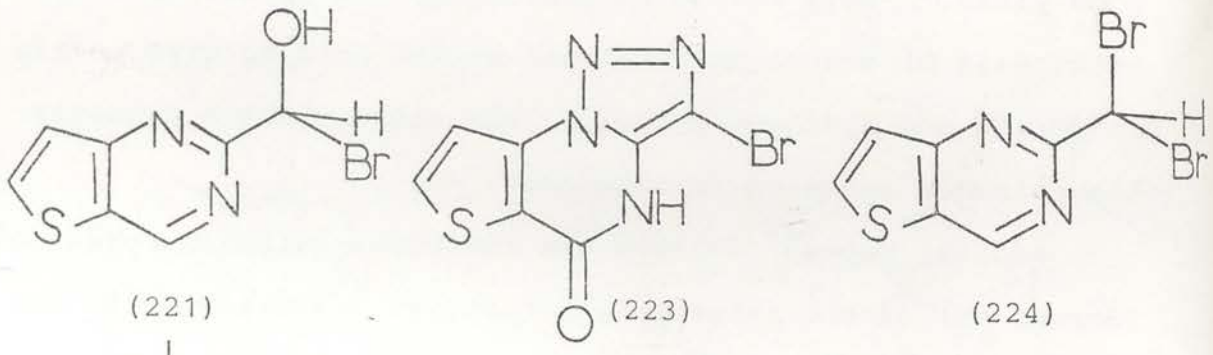
X

a; OAc

b; OH

c; Cl

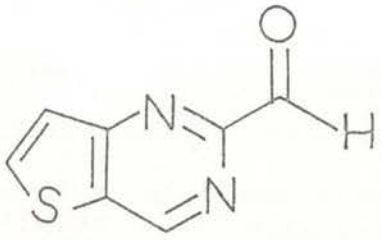
d; Br



(221)

(223)

(224)



(222)

(i) a; AcOH

b; H_2SO_4/H_2O

c; AcCl/AcOH

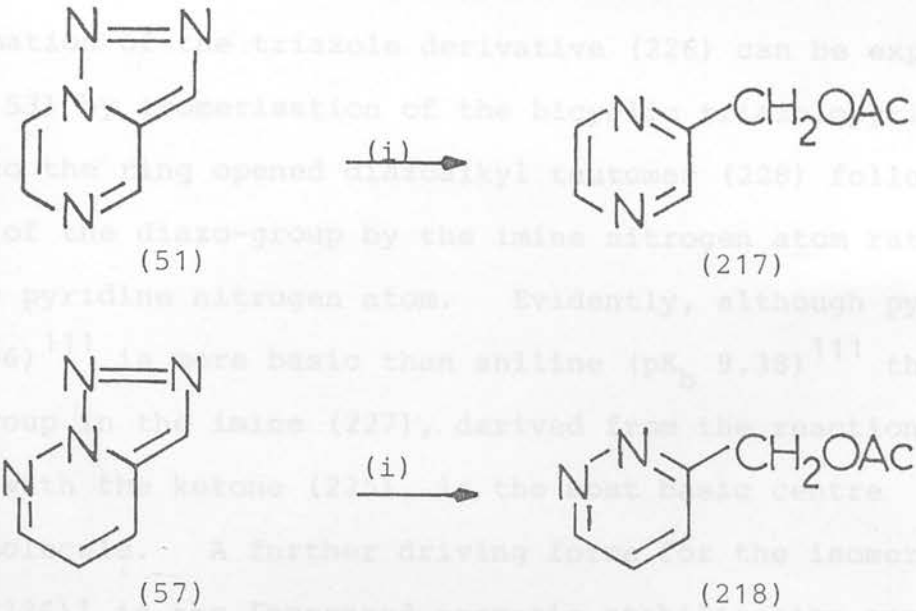
d; AcBr/AcOH

(ii) Br_2/NaOH

(iii) Br_2

Scheme 52

reported[36] to undergo acid-catalysed ring scission when heated in acetic acid to provide the acetoxymethyl derivatives (217) and (218) respectively and a similar reaction has been reported to occur on work up of triazolopyrazolopyrimidines in acetic acid.[53]



(51) (217)

(57) (218)

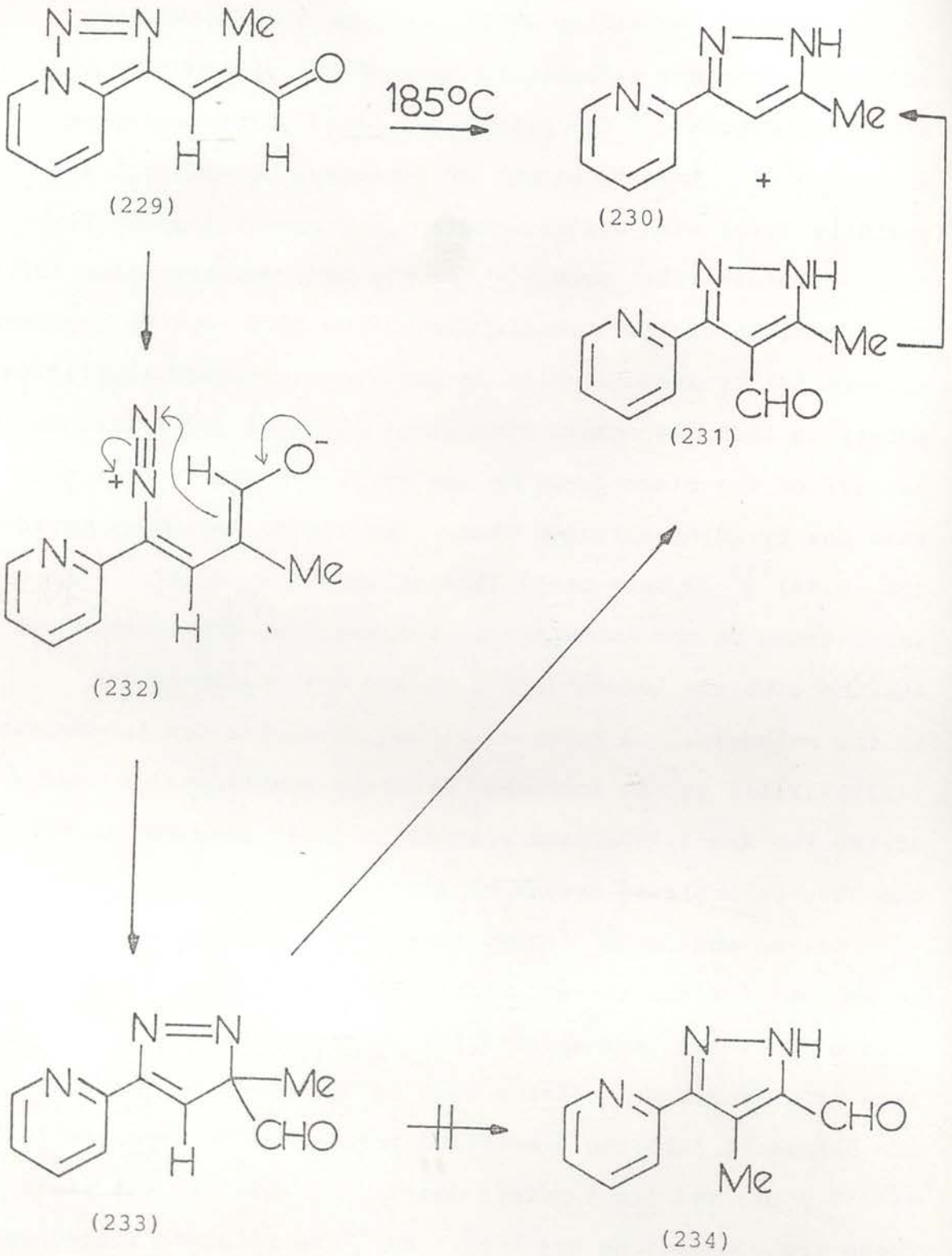
(i) AcOH

Scheme 51

Westerlund[100], although obtaining the expected acetoxythienopyrimidine (220a), hydroxythienopyrimidine (220b), chlorothienopyrimidine (220c) and bromothienopyrimidine (220d) on reaction of the fused triazole [Scheme 52; (219)] with the appropriate acid, found that, while bromination under neutral conditions did give the dibromothienopyrimidine (224), when basic conditions were employed neither the 1:1 halohydrin (221) nor its elimination product (222) was obtained. Instead the product (223) obtained was derived by bromination at the 3-position accompanied by oxidation (by HOBr) at the 5-position.

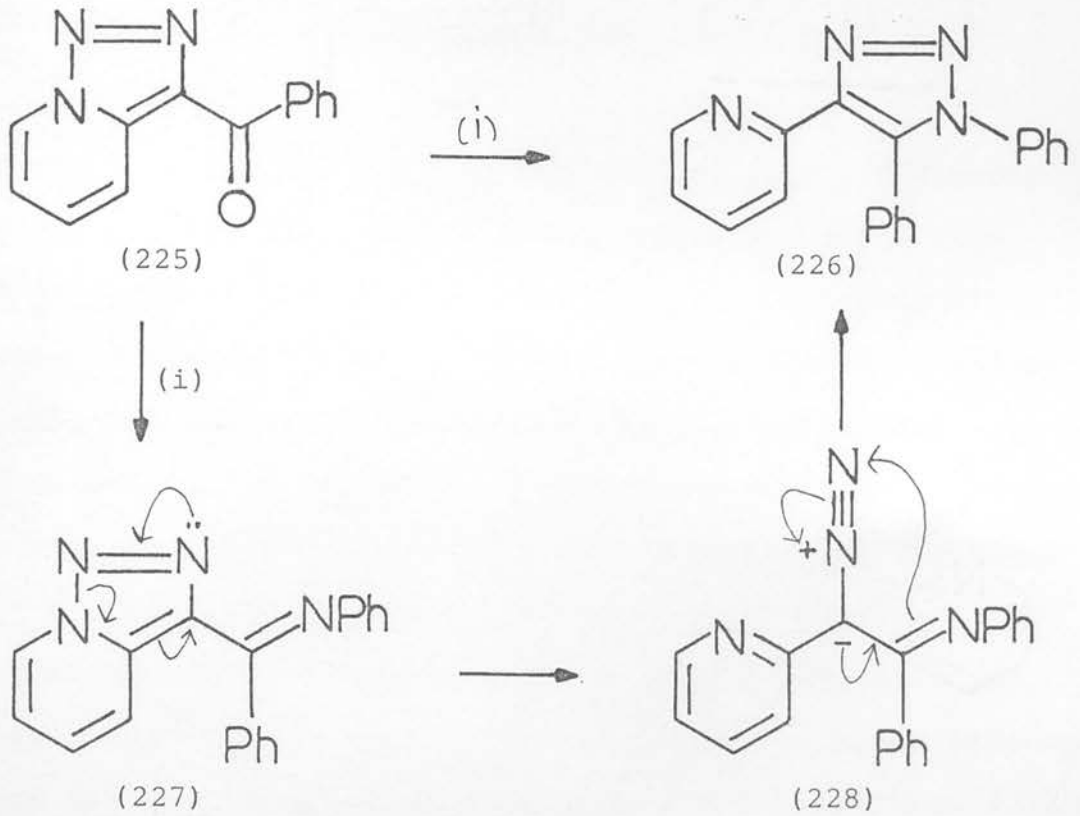
A type of reactivity which involves a diazo-species but which does not necessitate loss of the diazo-group has also been reported[38] for bridgehead-fused 1,2,3-triazoles (Scheme 53). Thus treatment of 3-benzoyltriazolo[1,5-a]-pyridine (225) with aniline gives 1,5-diphenyl-4-pyrid-2-yl-1,2,3-triazole (226) probably via the intermediate imine (227). The formation of the triazole derivative (226) can be explained (Scheme 53) by isomerisation of the bicyclic triazolopyridine moiety to the ring opened diazoalkyl tautomer (228) followed by capture of the diazo-group by the imine nitrogen atom rather than the pyridine nitrogen atom. Evidently, although pyridine (pK_b 8.96)[111] is more basic than aniline (pK_b 9.38)[111] the imino-group in the imine (227), derived from the reaction of aniline with the ketone (225), is the most basic centre in the molecule. A further driving force for the isomerisation [(227)→(226)] is the increased aromatic stabilisation energy of the two 6πe-delocalised systems in (226) compared to the one 10πe-delocalised system of (227).

Davies and Jones[112] have suggested a similar explanation to account for the thermal transformation (Scheme 54) of the triazolopyridine derivative (229) [whose synthesis by diazotisation of a 1-aminoquinolizium salt is described in Section 1.3.1(a); see Scheme 7] into the 3-methyl-5-pyrid-2-yl-1H-pyrazole (230) in 35% yield and its 4-formyl derivative (231) in 65% yield. These transformations are explained[112] by triazole ring-opening to the betaine (232) followed by pyrazoline ring closure to give the pyridylpyrazoline (233). An unexpected 1,5-formyl shift followed by aromatization of the pyrazole ring then accounts for the major product (231) which yields the minor product (230)



(229) (230) (231) (232) (233) (234)

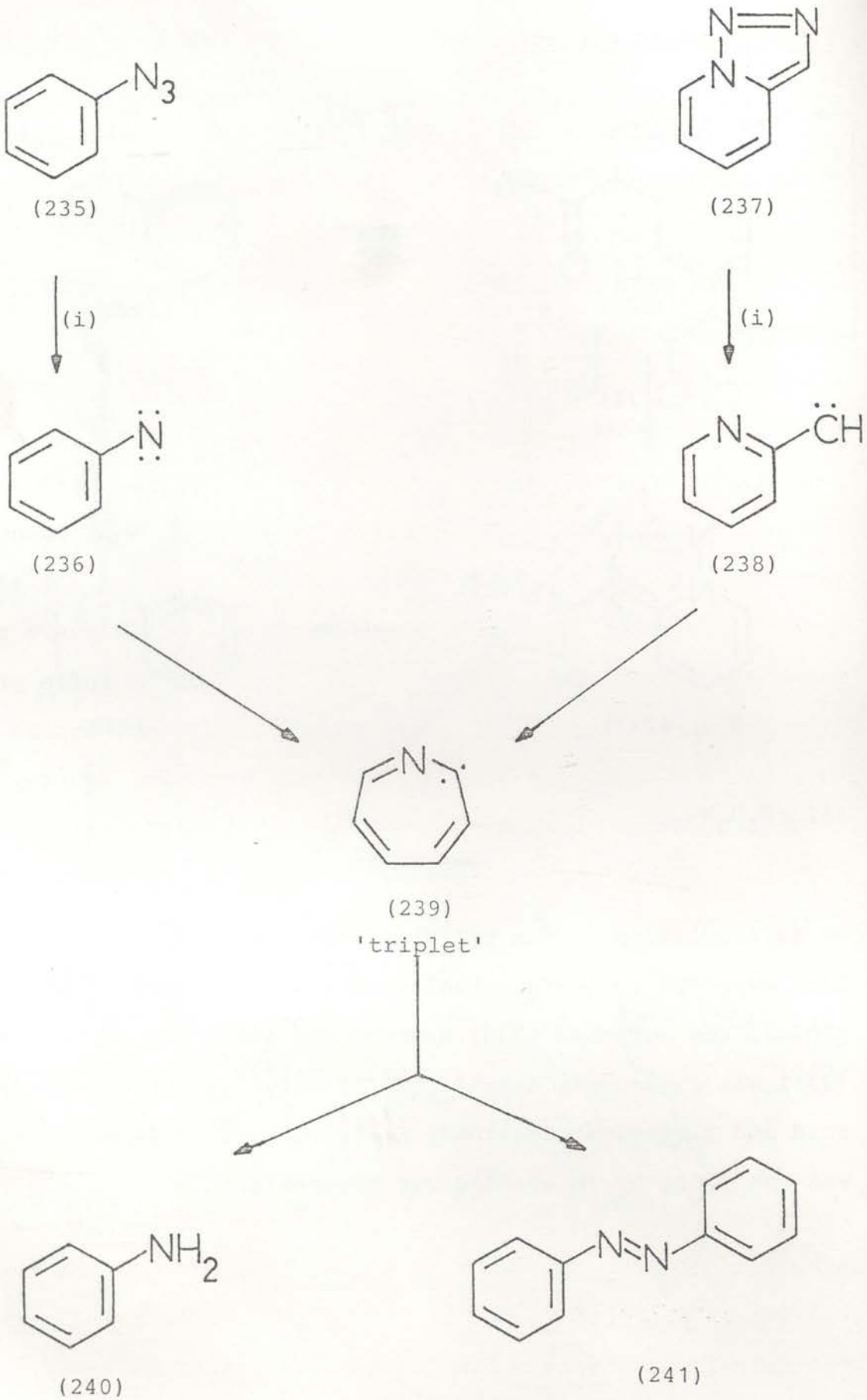
Scheme 54



(i) $C_6H_5NH_2$

Scheme 53

by deformylation. The pyridylpyrazoline (233) might have been expected to preferentially undergo a 1,5-methyl shift to produce the compound (234) however the structure of the product (231) was rigorously established by oxidation to the corresponding acid and subsequent decarboxylation to give (230) whose structure was confirmed by an unambiguous synthesis.



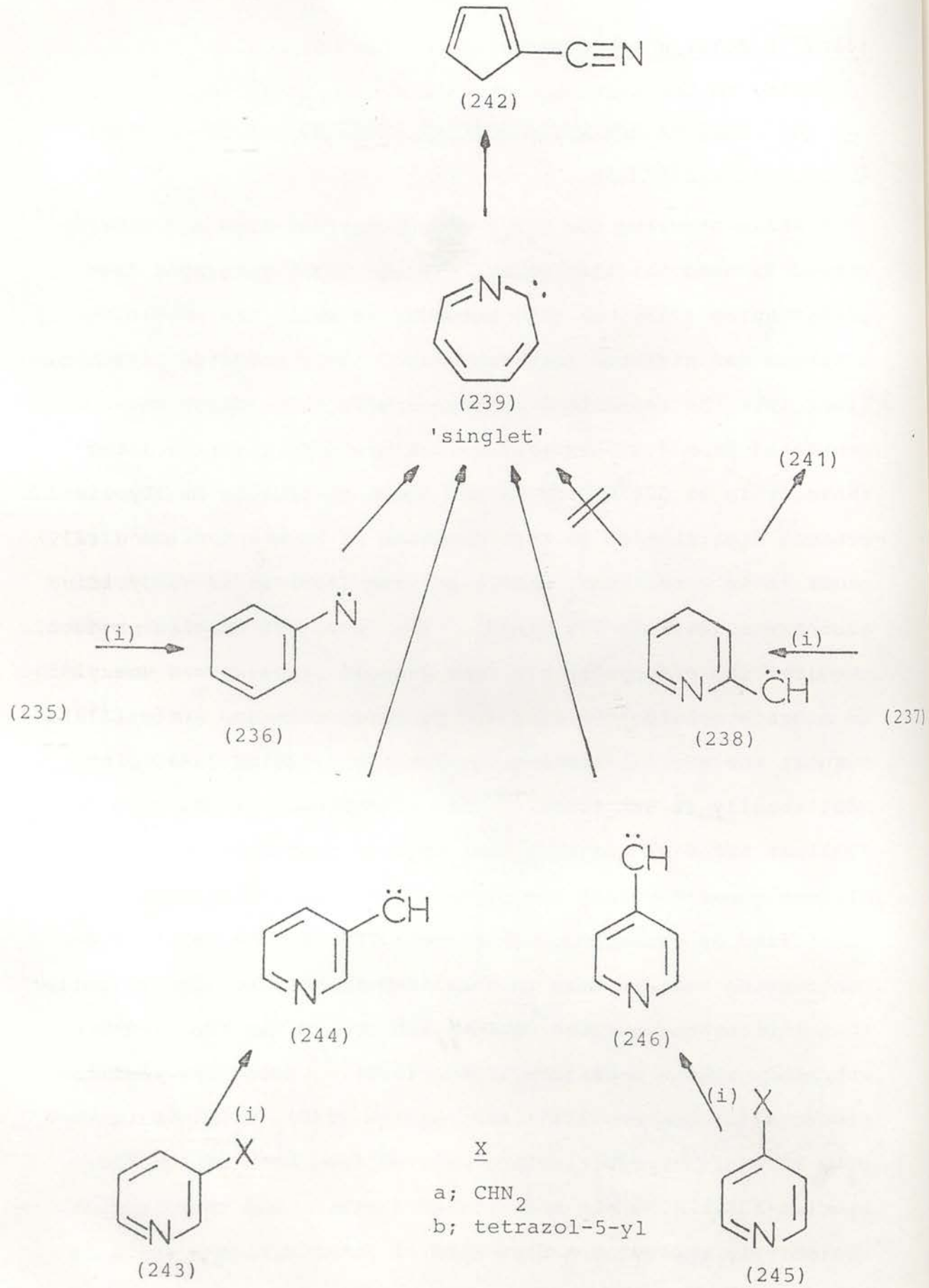
(i) 500°C/0.04 mmHg; slow rate of introduction

Scheme 55

1.4.2 Homolytic Reactivity

(a) Thermal and photochemical reactions of bridgehead-fused 1,2,3-triazoles

While studying the C_6H_5N energy surface Crow and Wentrup[101] showed (Scheme 55) that phenyl nitrene (236) generated from phenyl azide (235) can give products in which the exocyclic nitrogen has migrated into the ring. This prompted investigations into the isomeric 2-pyridylcarbene (238) which was generated from 1,2,3-triazolo[1,5-a]pyridine (237) by 'mild' thermolysis at 500°C/0.04 mm and found to provide an identical product distribution to that expected of phenyl nitrene (236) under these conditions, namely aniline (240) in 4% yield and azobenzene (241) in 77% yield. The formation of these products requires the endocyclic nitrogen atom of 2-pyridylcarbene (238) to migrate outside the ring and prompted Crow and Wentrup[101] to suggest the carbene-nitrene equilibrium [(236)$\rightleftharpoons$(238)]. Additionally it was found[113] that thermolysis of phenyl azide (235) at 600-970°C using a fast rate of introduction of the nitrene generator into the furnace provided a different product identified as cyanocyclopentadiene (242) (Scheme 56). These contrasting results were rationalised firstly by the suggestion[102] that the carbene-nitrene equilibrium occurs via the ring-expanded carbene 2-azatropylidene (239). Secondly, that the products [azobenzene (241) and aniline (240)] obtained using a slow rate of introduction are derived from each of the three species (236), (238) and (239) in the triplet state. And thirdly that thermolysis employing a fast rate of introduction results in the initial generation of the azatropylidene (239) in a hot-



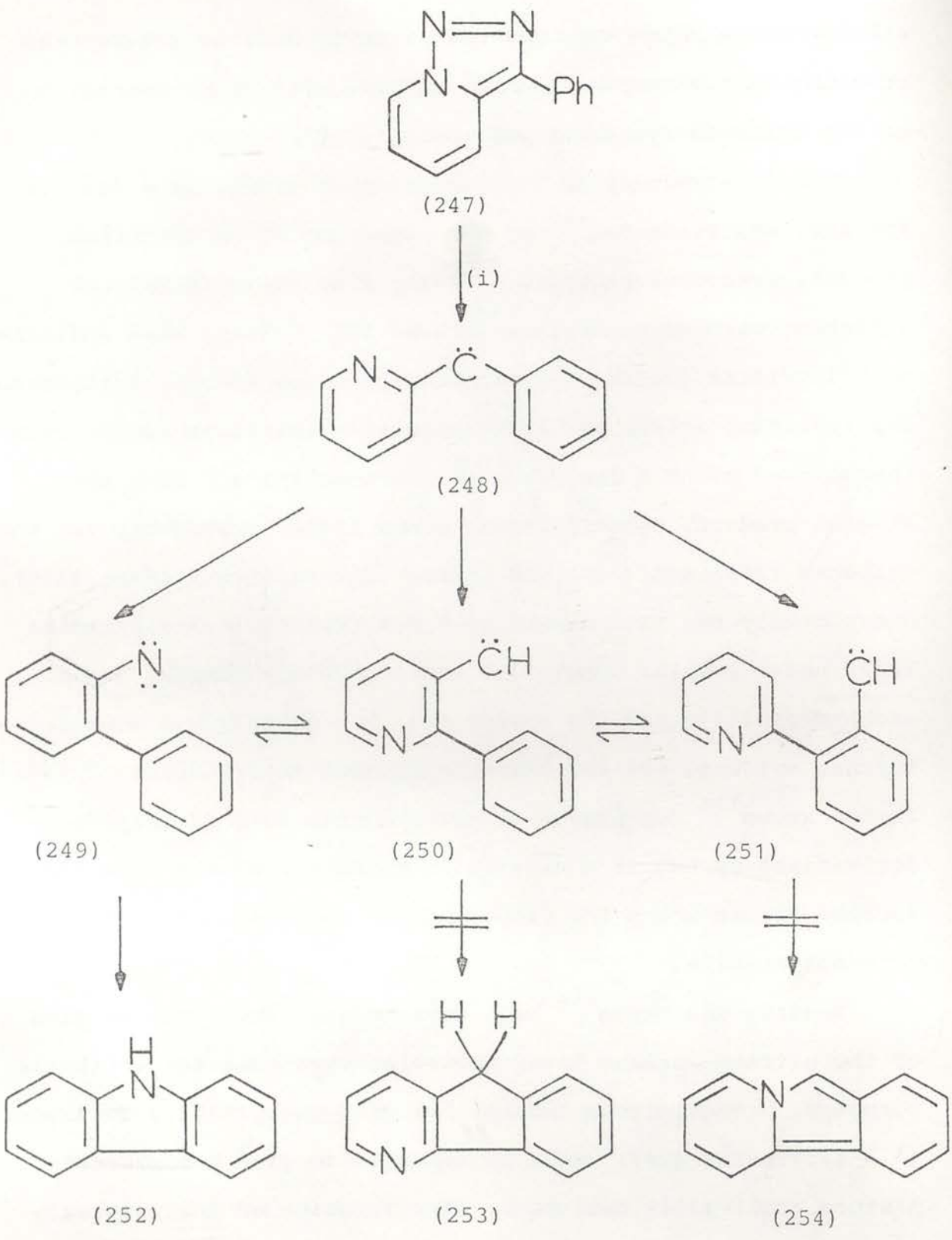
(i) 600-900°C/0.1 mmHg; fast rate of introduction

Scheme 56

singlet state which does not have time to undergo intersystem crossing to the triplet species and therefore ring-contracts to the observed cyanocyclopentadiene product (242).

The intermediacy of 2-azatropylidene (239), as a singlet species, was evidenced[103] by the formation of an identical product, cyanocyclopentadiene (242), from the pyrolysis of different carbene generators (Scheme 56). Thus, when 3-diazomethylpyridine (243a), 4-diazomethylpyridine (245a), 3-(tetrazol-5-yl)pyridine (243b) and 4-(tetrazol-5-yl)pyridine (245b) were thermolysed using a fast rate of introduction all gave the singlet product, cyanocyclopentadiene (242), presumably via the carbenes (244) and (246) and thence the 2-azatropylidene (239). Unexpectedly the thermolysis of 1,2,3-triazolo[1,5-a]pyridine (237) under similar conditions still gave the triplet product, azobenzene (241) and the reason for this anomaly was unexplained. Further evidence for the 2-azatropylidene intermediate (239) is the known[114] conversion of nitrobenzene into 3H-azepine derivatives by way of a nitrene intermediate of the type (236) (Scheme 55) in which the ring-expanded intermediate is trapped by a nucleophile.

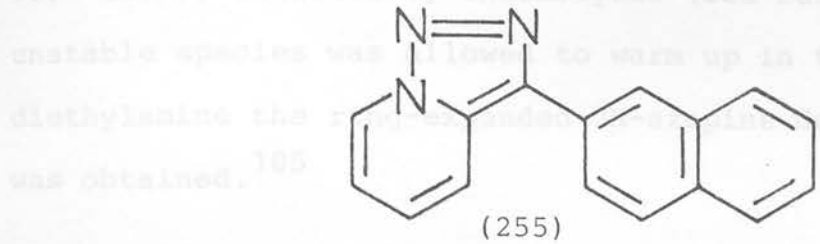
Wentrup and Mayor[104] have demonstrated the peculiarities of the nitrene-carbene interconversion when used for synthetic purposes. Thermolysis (Scheme 57) of 3-phenyl-1,2,3-triazolo-[1,5-a]pyridine (247) would be expected to give the product mixture (252)-(254) derived by equilibration of the initially generated carbene (248) with the nitrene (249) and the carbenes (250) and (251). However in practice the carbazole (252) was isolated exclusively in greater than 90% yield. In contrast (Scheme 58) pyrolysis of the 3-(naphth-2-yl)triazolo-



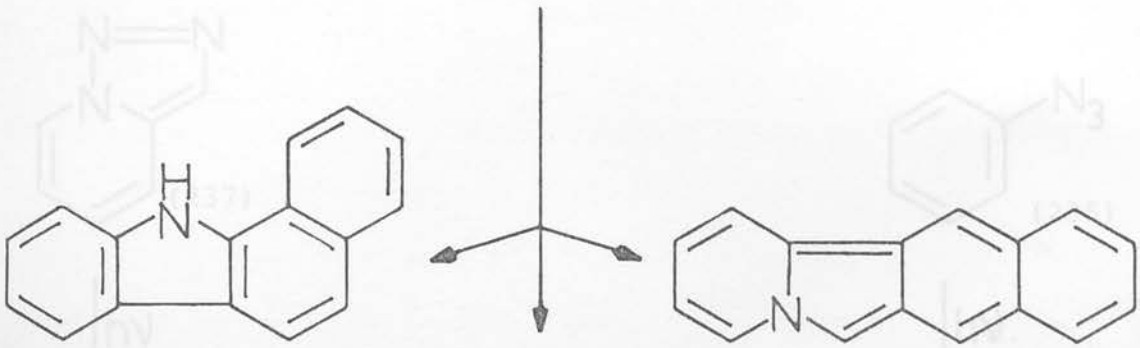
(i) 380-390°C/0.01 mmHg

Scheme 57

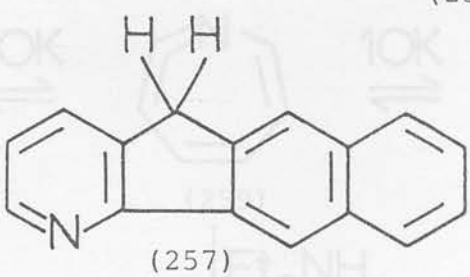
[1,5-a]pyridine (255) is reported to give all three products (256)-(258) in respective yields of 30%, 16% and 48% and hence such equilibration of intermediates must be operating in this case.



(255)



(256) (258)

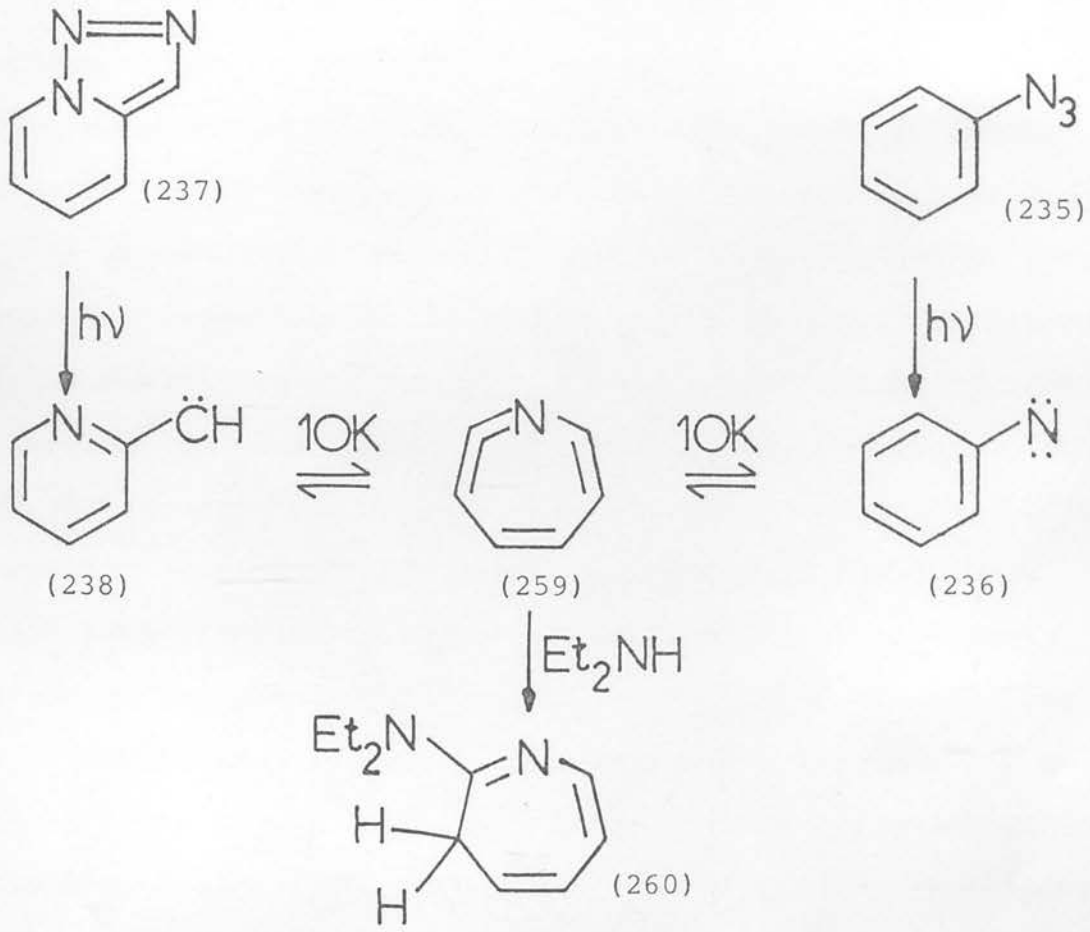


(257)

Scheme 58

Photolysis of both 1,2,3-triazolo[1,5-a]pyridine (237) (Scheme 59) and phenyl azide (235) in non-nucleophilic solvents has been observed to give products identical to those obtained by mild thermolysis (i.e. azobenzene and aniline) suggesting that the equilibrium [(236)$\rightleftharpoons$(238)] can also be induced photolytically. In fact Chapman and his co-workers[105] have shown that both the phenylnitrene (236) generator (235) and the 2-pyridylcarbene (238) generator (237) when photolysed in an argon

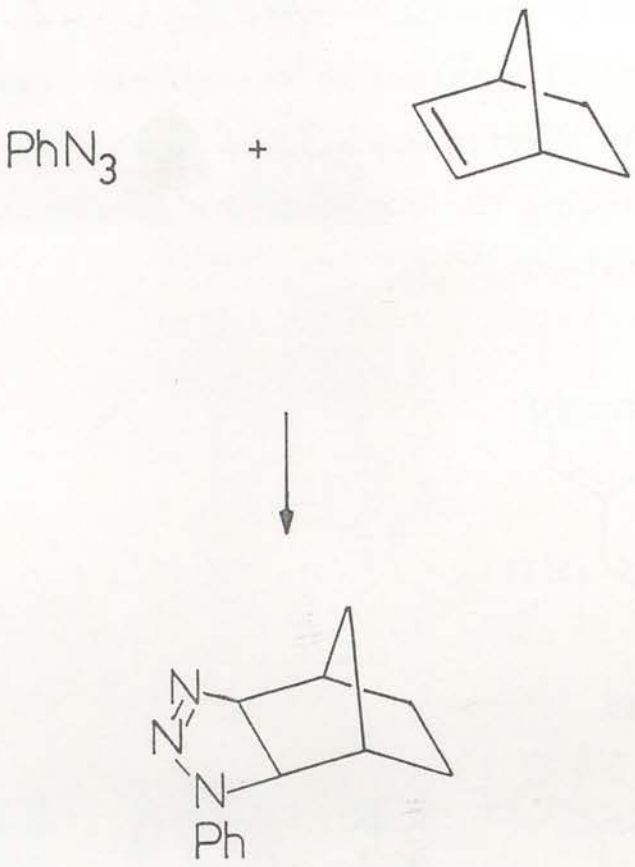
matrix at 10K give the same product and by studying this species spectroscopically have inferred its structure to be the cyclic ketenimine (259) and not the azatropylidene [Scheme 55; (239)] obtained by thermolysis (see before). When the unstable species was allowed to warm up in the presence of diethylamine the ring-expanded 3H-azepine derivative (260) was obtained.[105]



Scheme 59

(b) Thermal and photochemical reactions of bridgehead-fused 1,2,3-triazolines

It has generally been recognised[91,115] that for non-bridgehead-fused triazolines thermal decomposition leads to



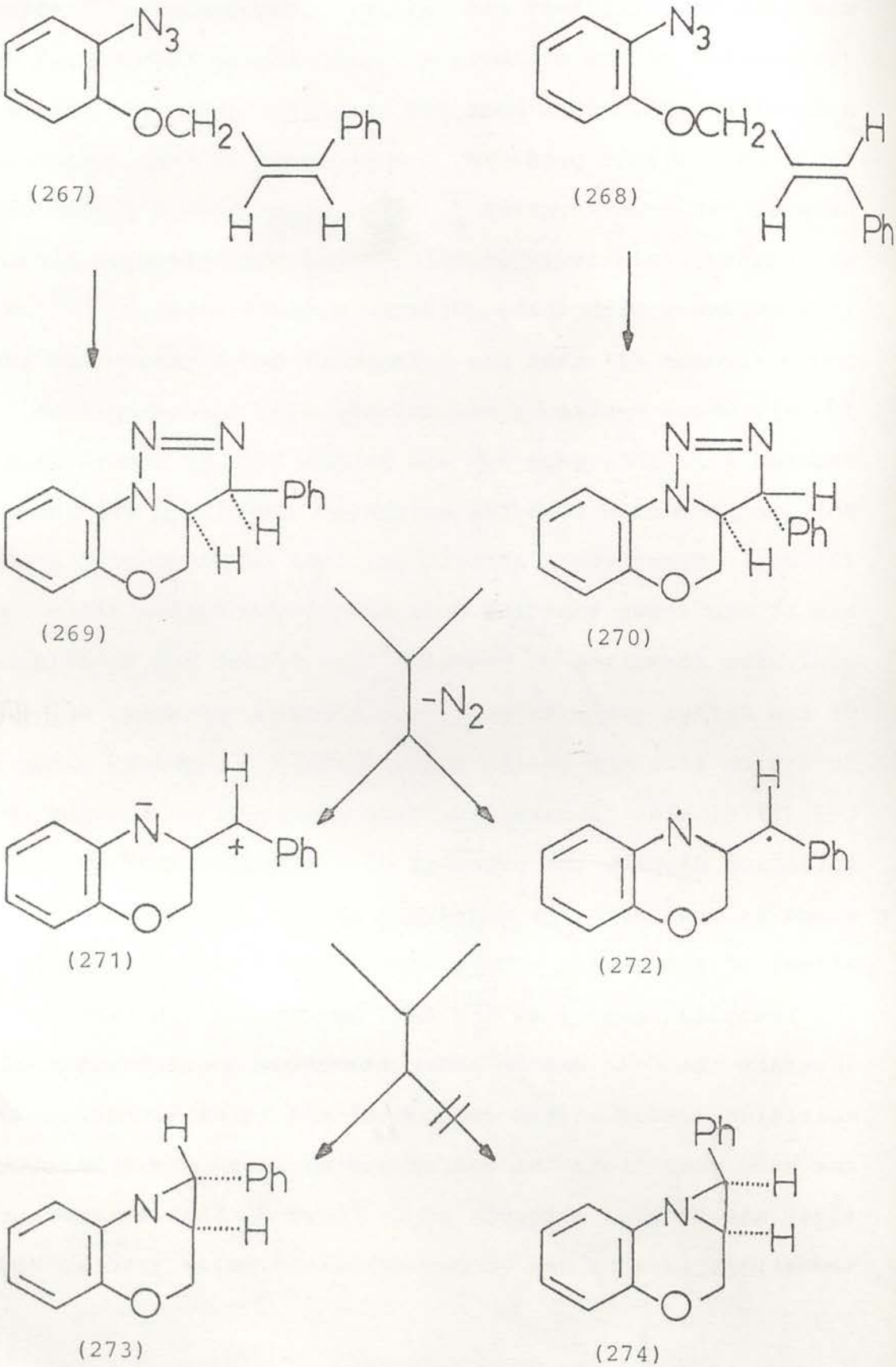
(261)

(262)

(263)

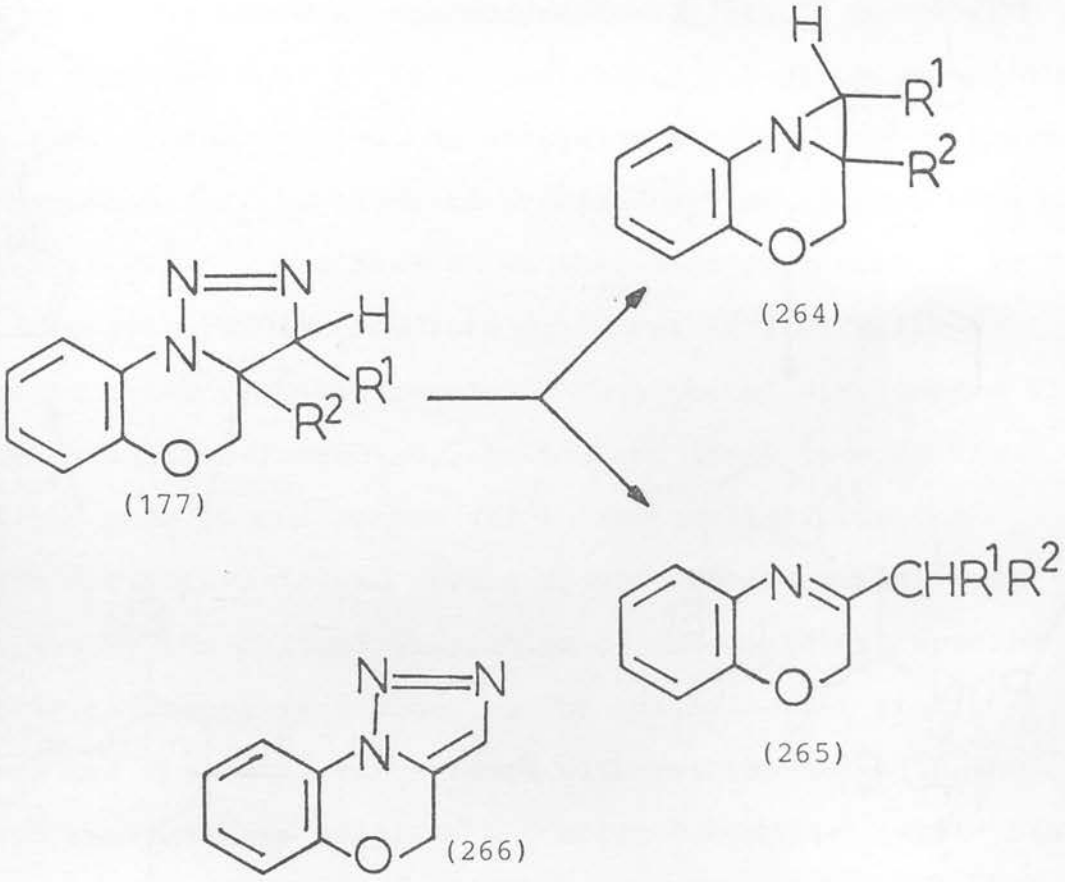
Scheme 60

mixtures of aziridines and imines. For instance[116] thermolysis (Scheme 60) of the triazoline (261), formed from phenyl azide and norbornene, gives both the aziridine (262) and the imine (263) as isolable products. Photolysis of such triazolines however has been reported[117-119] to give higher yields of aziridines, relatively uncontaminated with isomeric products. In accordance with these reports, several workers[75,87] have found (Scheme 61) that the bridgehead-fused triazoline compound (177a), whose synthesis has already been discussed [see Section 1.3.3(b), page 26 and Scheme 39], on thermolysis in solution produced both the aziridine (264a) and the imine (265a). Substituent effects for this reaction were studied and it was shown that the C-3a methyl derivative (177b) gave exclusive formation of the aziridine (264b) due to reluctance of the methyl group to undergo migration necessary for transformation into the cyclic imine (265b). A phenyl group at C-3 (177c) also favours aziridine formation as opposed to imine formation despite the presence of a hydrogen atom at C-3a which is available for migration to give the imine (265c). The effect of the phenyl substituent is presumably to stabilise the benzylic radical at C-3 thus decreasing its tendency to abstract the C-3a H-atom hence promoting the formation of the aziridine (264c) at the expense of the imine (265c). Under the same conditions the corresponding fused aromatic triazole (266) was stable, although it is known[120] that monocyclic aromatic triazoles can be converted thermally into azirenes.


N3
OCH2
Ph
H
H
(267)
N3
OCH2
H
H
Ph
(268)
N=N
N
Ph
H
H
(269)
N=N
N
H
Ph
H
(270)
-N2
H
N
+
Ph
(271)
H
N
Ph
(272)
H
Ph
N
H
(273)
Ph
H
N
H
(274)

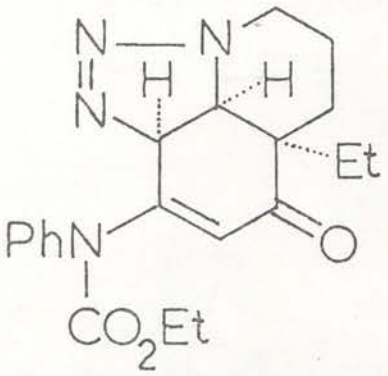
Scheme 62

	R^1	R^2
a;	H	H
b;	H	Me
c;	Ph	H



Scheme 61

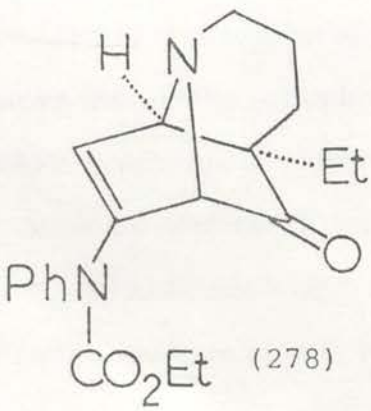
Chou and Smith[87] have further shown (Scheme 62) that both the *cis*- and *trans*-phenyl substituted triazolines (269) and (270), derived from the *cis*- and *trans*-phenyl substituted allyl ethers (267) and (268), on thermolysis give the same *trans*-aziridine (273). Although the *trans*-aziridine (273) could be formed by a concerted mechanism from the *trans*-triazoline (270) the fact that none of the *cis*-aziridine (274) is formed from the *cis*-triazoline (269) implies the existence



(183)

(i)

(277)

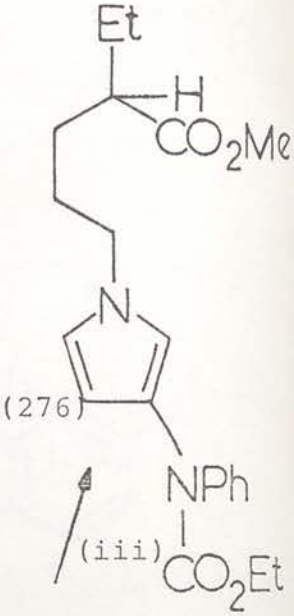


(278)

dimer

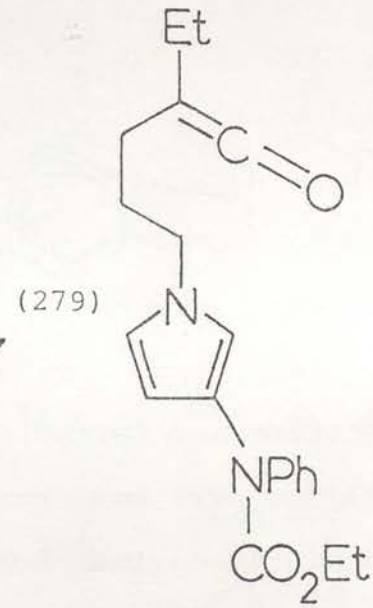
(275)

(ii)



(276)

(iii)



(279)

(i) hν

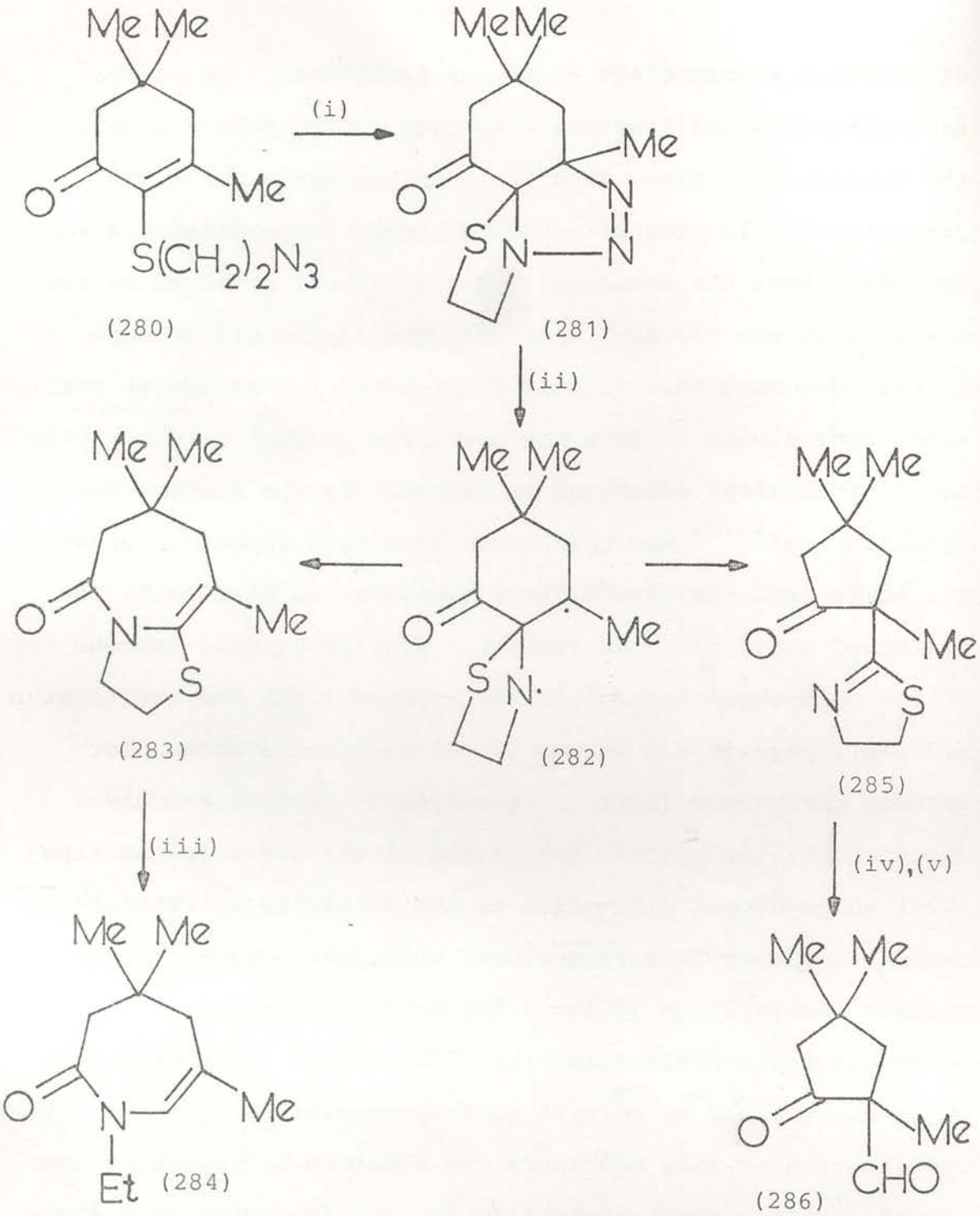
(ii) Benzene

(iii) MeOH

Scheme 63

of a common intermediate which was formulated[87] as either the zwitterion (271) or the diradical (272), more probably the latter.[121] Since free rotation can occur about the exocyclic double bond of either proposed intermediate it was deduced[87] that the *trans*-aziridine (273) was obtained in both cases as it was the most thermodynamically stable product. Further evidence that it is a short-lived 1,3-diradical species which ring closes to give the aziridine product in such thermal and photochemical reactions is provided by the elegant work of Schultz *et al*[93,94] who have shown that when formation of an aziridine from the intermediate diradical is sterically inhibited other products result. Thus photolysis (Scheme 63) of the bridgehead-fused 1,2,3-triazoline (183) [see Section 1.2.3(b), page 26 and Scheme 40] in methanol affords the pyrrole derivative (276). This drastic rearrangement was explained by the initial generation of the diradical species (277) which cannot ring-close to the aziridine for steric reasons and therefore ring-closed with rearrangement to the bridged intermediate (278). The bridged compound (278) then underwent retro-Diels-Alder reaction to give the ketene (279) which was trapped by solvent thereby forming the product (276). Confirmation of this mechanism was obtained by repeating the photolysis in a non-nucleophilic solvent (benzene) whence the ketene dimer (275) was isolated.

Reactions which provide ring-expanded or ring-contracted products are of potential synthetic use and therefore examples in which both expansion and contraction are observed are extremely interesting. A striking example (Scheme 64) of such a reaction[93] is the transformation of the azide (280)



(i) heat, xylene

(ii) hν, methanol

(iii) nickel boride

(iv) aluminium, wet ether

(v) mercuric chloride

Scheme 64

into a 1:1 mixture of the ring-expanded thiazolidino-tetrahydroazepinone (283) and the ring-contracted thiazolyl-cyclopentanone (285). A possible mechanism of this reaction might involve thermal cycloaddition to form the bridgehead-fused 1,2,3-triazoline (281) followed by photolytic extrusion of nitrogen to give the diradical intermediate (282). As in the previous example aziridine formation is precluded on steric grounds therefore rearrangement occurs with competing acyl migration to both radical centres hence affording both products (283) and (285). An alternative mechanism involving concerted acyl migration with loss of nitrogen is also possible. The structure of the ring-expanded thiazolidine-fused azepinone (283) was proved by using nickelboride desulphurization to give the monocyclic azepinone (284) thus providing a method for conversion of the cyclohexanone derivative (280) into the higher homologous enaminone (284). Confirmation of the ring-contracted cyclopentanone structure (285) was also obtained by removal of the thiazolidine ring to give the known aldehyde (286).

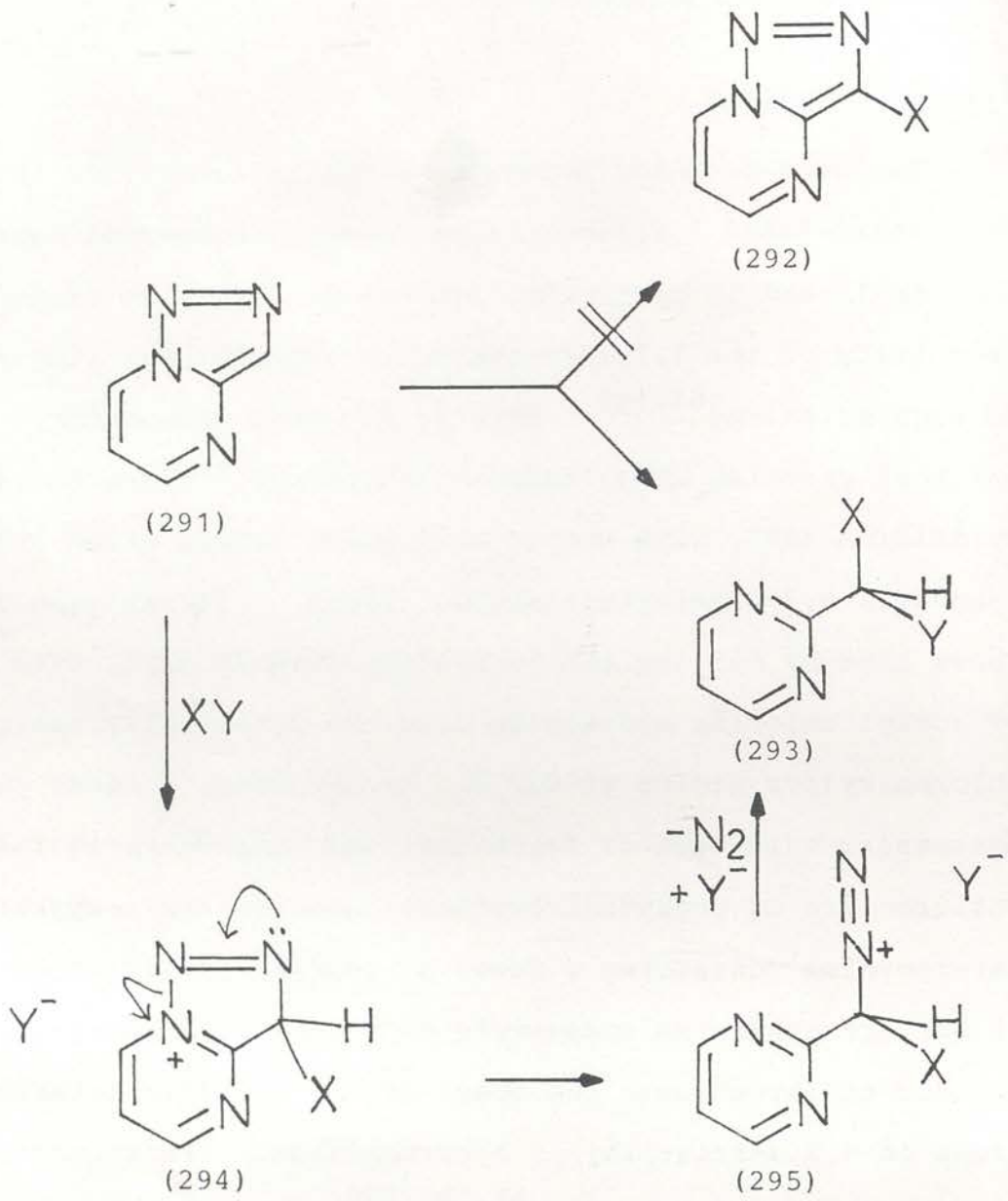
Chapter 2

Some Studies on the Acid-promoted Ring Cleavage Reactions of Bridgehead-fused 1,2,3-Triazole Derivatives

Some Studies on the Acid-promoted Ring Cleavage Reactions of 1,2,3-Triazolo[1,5-a]pyrimidines

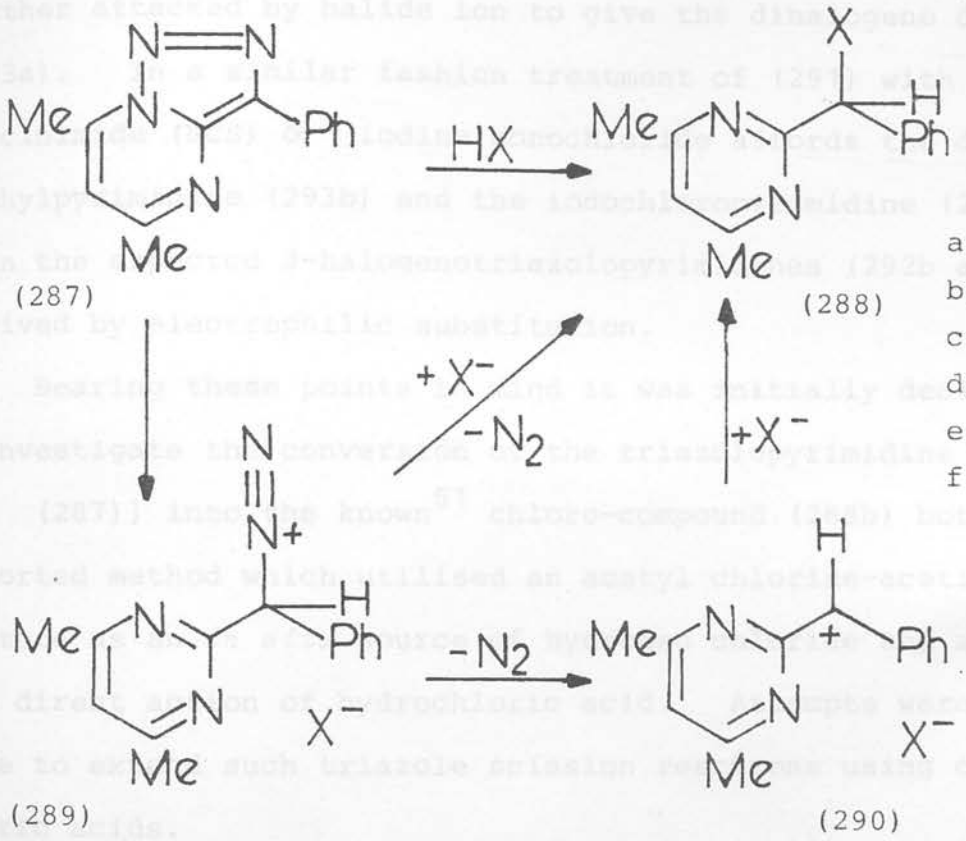
2.1 Introduction

The acid-promoted scission of the triazole ring in bridgehead-fused 1,2,3-triazoles is well documented (see Chapter 1) and in particular several workers have studied the reactivity of the 1,2,3-triazolo[1,5-a]pyrimidine ring system to such scission.[61,109] Thus it has been demonstrated (Scheme 65) that reaction of 5,7-dimethyl-3-phenyl-1,2,3-triazolo[1,5-a]-pyrimidine (287) with acetic acid under reflux gives 2-(α-acetoxybenzyl)-5,7-dimethylpyrimidine (288a). It has also been shown that by heating the triazolopyrimidine (287) with a mixture of acetyl chloride and acetic acid the potentially useful 2-chloroalkylpyrimidine (288b) can be obtained. Since pyrimidines possessing this type of functionalised side chain at the 2-position are of potential synthetic use for the preparation of heterocycles containing a fused pyrimidine nucleus (see Chapter 3) but are otherwise accessible only with difficulty it was decided to investigate the scope of the triazole scission reactions of 1,2,3-triazolo[1,5-a]pyrimidines. Furthermore several pathways have been proposed[61,100,109] for such triazole scission reactions and it was hoped that a study of this type might give additional insight into the mechanism by which scission proceeds. 1,2,3-Triazolo[1,5-a]pyrimidine derivatives were chosen as substrates for the study because of their ready availability in high yield and also because it had already been demonstrated that the triazole ring in such polyazaheterocycles is susceptible to cleavage on treatment with acidic reagents. Thus, in accord



	X	Y
a;	Br	Br
b;	Cl	Cl
c;	I	Cl

Scheme 66



Scheme 65

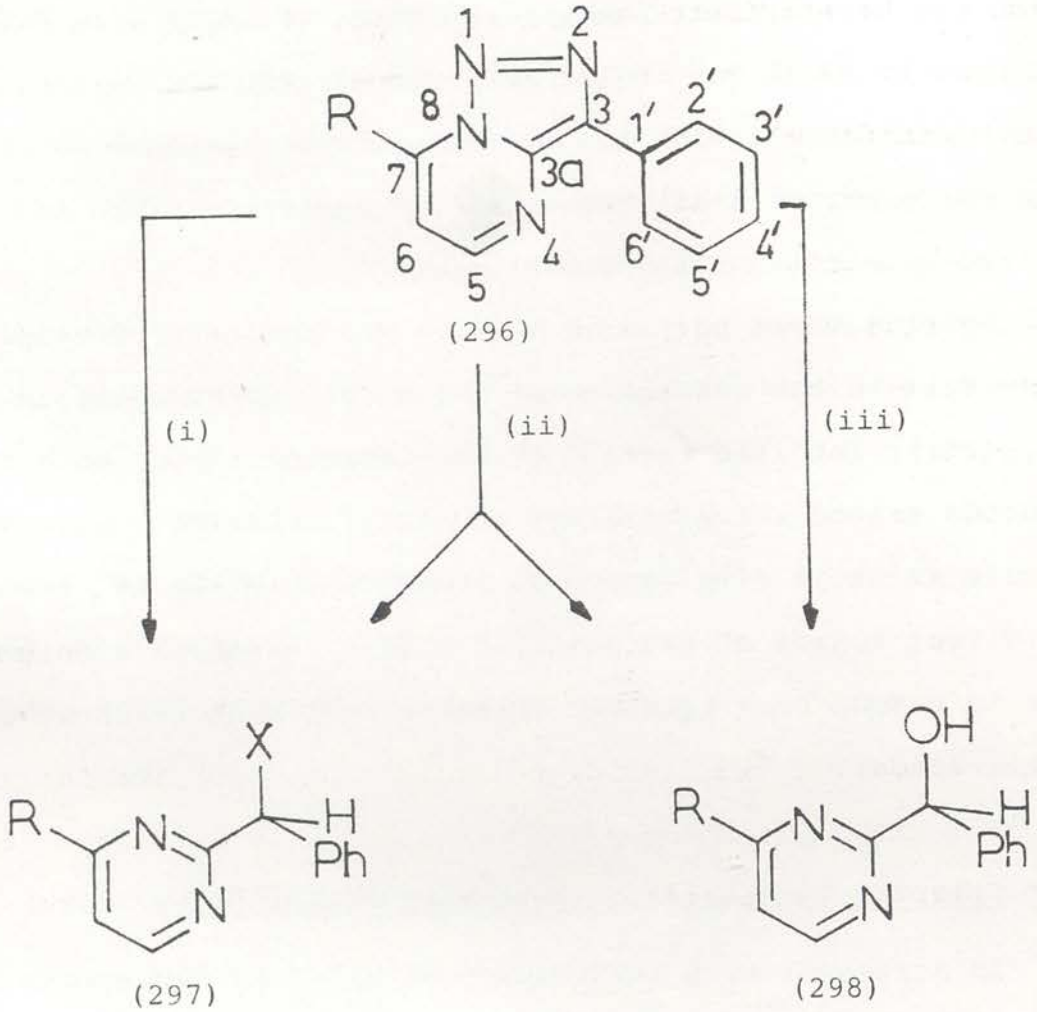
with the general reactivity to triazole scission described earlier (see Chapter 1, Section 1.4.1) the triazolopyrimidine (287) has also been observed[61] to undergo hydrolytic ring-opening in dilute sulphuric acid to afford the alcohol (288e). In addition Novinson[109] and his co-workers have recently investigated the ability of halogenating agents to promote triazole ring-opening of 1,2,3-triazolo[1,5-a]pyrimidines. Both bromine and *N*-bromosuccinimide (NBS) are reported (Scheme 66) to convert the triazolopyrimidine (291) into the dibromomethylpyrimidine (293a) instead of the expected 3-bromotriazolopyrimidine (292a) suggesting that the intermediate cation (294) undergoes preferential ring opening to the diazonium cation (295) rather than proton-loss to give the substituted triazolopyrimidine (292a). The diazonium cation (295) is then

further attacked by halide ion to give the dihalogeno derivative (293a). In a similar fashion treatment of (291) with *N*-chlorosuccinimide (NCS) or iodine monochloride affords the dichloromethylpyrimidine (293b) and the iodochloropyrimidine (293c) rather than the expected 3-halogenotriazolopyrimidines (292b and 292c) derived by electrophilic substitution.

Bearing these points in mind it was initially decided to reinvestigate the conversion of the triazolopyrimidine [Scheme 65; (287)] into the known[61] chloro-compound (288b) both by the reported method which utilised an acetyl chloride-acetic acid mixture as an *in situ* source of hydrogen chloride and also by the direct action of hydrochloric acid. Attempts were then made to extend such triazole scission reactions using other protic acids.

2.2 Triazole Ring Scission Involving Protic Acids

In agreement with the results obtained by Sutherland and Tennant[61] it was found in the present studies that the chloro-compound (288b) could be obtained (Scheme 65) in quantitative yield by heating the triazolo-pyrimidine (287) in a mixture of acetyl chloride and acetic acid. The same compound (288b) was also produced when the triazolopyrimidine (287) was heated under reflux in ethanol containing hydrochloric acid, albeit in lower yield. However also formed in this reaction was a minor product which was shown by elemental and mass spectral analysis to have the molecular formula $C_{15}H_{18}N_2O$. The assignment of the 4,6-dimethyl-2-(α-ethoxybenzyl)pyrimidine structure [Scheme 65; (288f)] to this compound was confirmed by its ^1H n.m.r. spectrum



	R	X
a;	H	Cl
b;	Me	Cl
c;	H	Br

(i) AcCl/AcOH

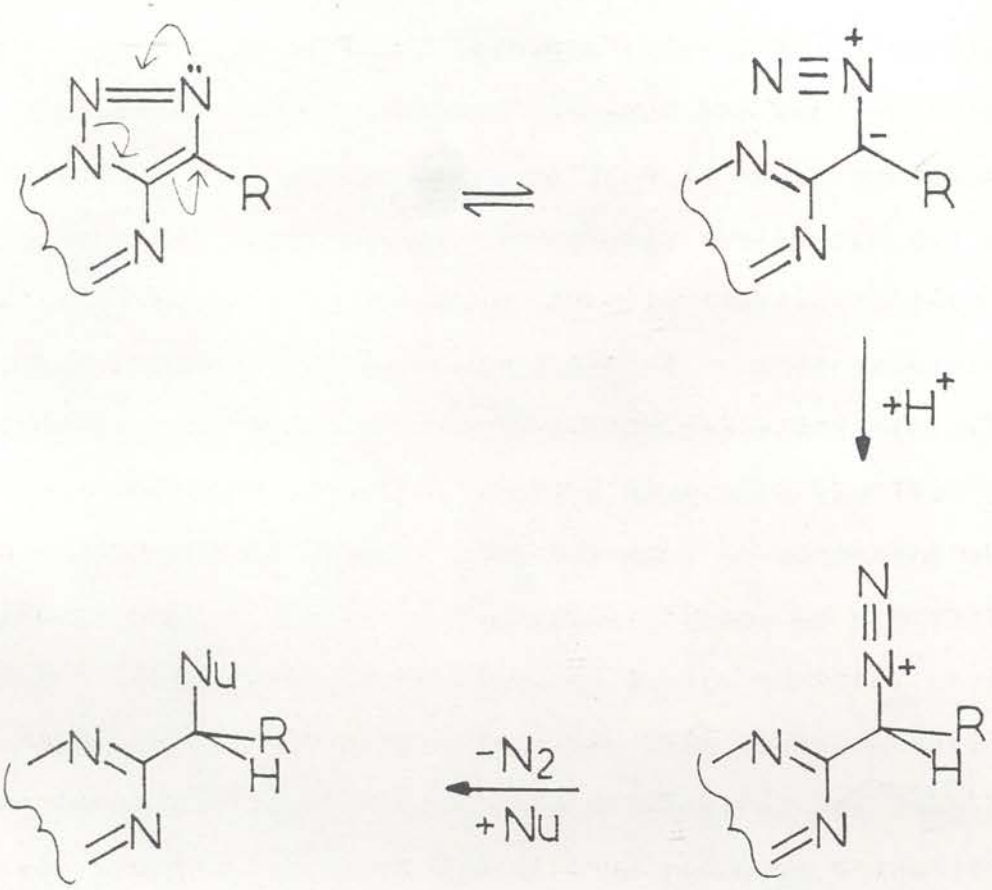
(ii) conc.HX/room temperature

(iii) conc.HCl/heat

Scheme 67

which showed the presence of a one-proton singlet at δ5.52 which can be attributed to a benzylic CH group thus demonstrating that triazole ring cleavage had occurred. The ^{1}H n.m.r. also contained the expected triplet-quartet resonances due to the ethoxy group as well as a six-proton singlet assignable to the two equivalent ring methyl groups and a one-proton aromatic singlet consistent with the presence of a 2,4,6-trisubstituted pyrimidine ring. It has been proposed[50] that on protonation in acidic media bridgehead-fused 1,2,3-triazole compounds such as (287) may ring open to form a diazonium cation [e.g.(289)]. Thus formation of both the chloro-compound (288b) and the ether (288f) can be readily explained by attack on the diazonium cation (289) by either chloride anion or ethanol. However it is also possible that the diazonium cation (289) initially loses nitrogen and it is solvolysis of the resulting carbonium ion (290) which produces both of the isolated products (288b) and (288f).

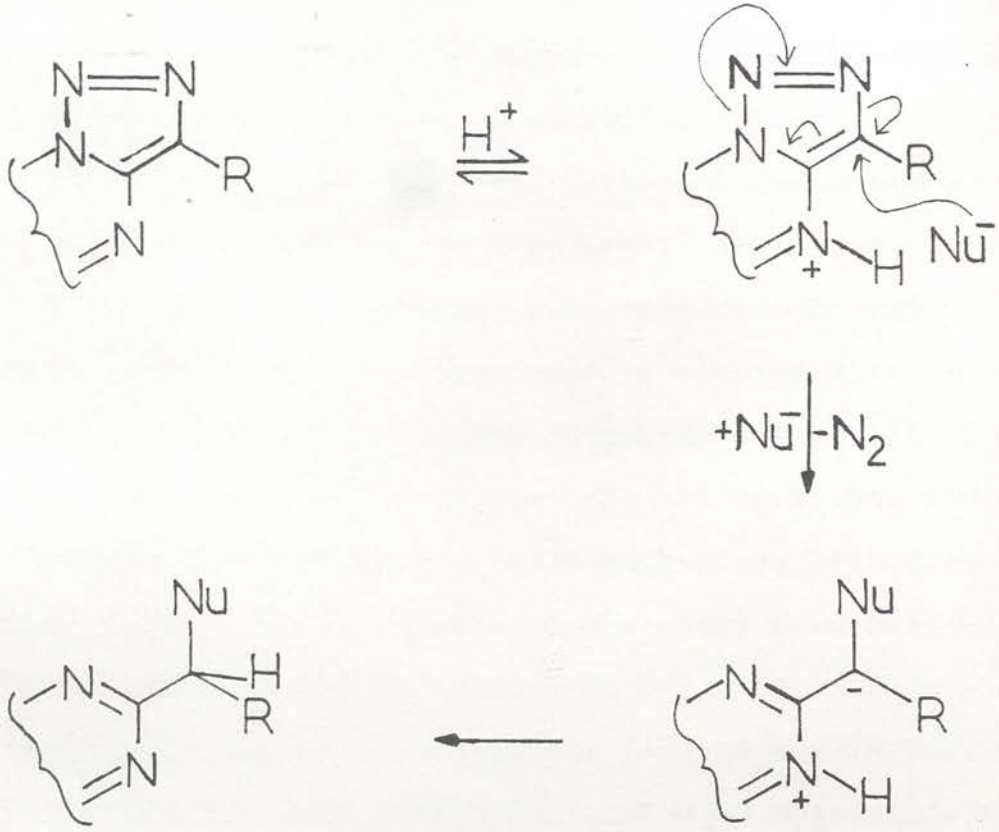
To provide further examples of chlorinative scission of the triazolopyrimidine ring system (Scheme 67) the known[122] monomethyl (296b) and 4,6-unsubstituted (296a) analogues of the previously studied dimethyltriazolopyrimidine [Scheme 65; (287)] were prepared. Triazole ring scission of these compounds employing acetyl chloride-acetic acid provided the respective chlorobenzylpyrimidines (297b) and (297a) whose properties were entirely consistent with the assigned structures. Alternatively the triazolopyrimidine (296a) when dissolved in hydrochloric acid with no co-solvent and without elevation of temperature was also converted smoothly into the chloro-compound (297a). Similar treatment of the monomethyltriazolopyrimidine (296b)



Scheme 68

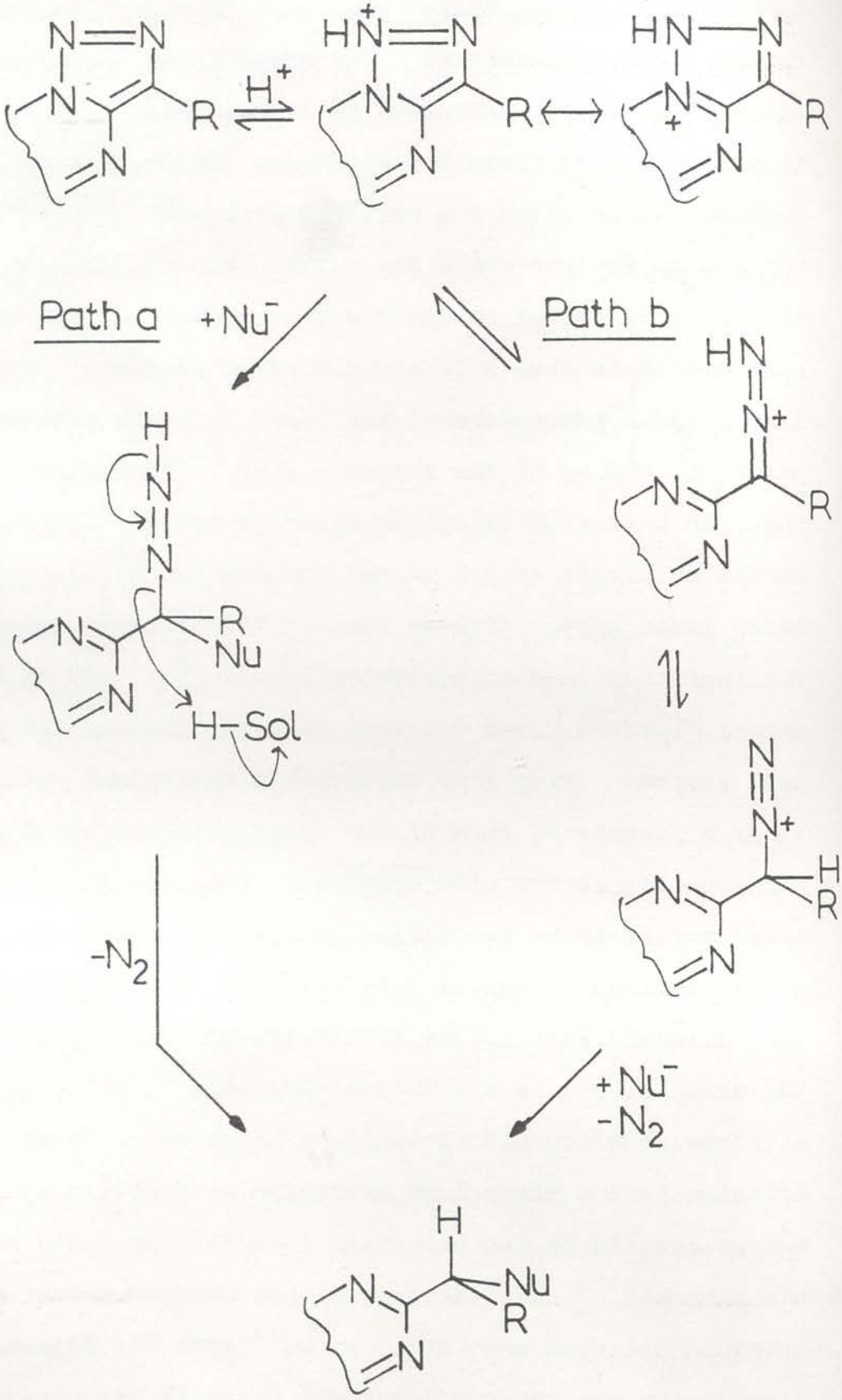
yielded the chlorobenzylpyrimidine (297b) as well as a by-product whose i.r. spectrum suggested it was an alcohol (ν_{max} OH 3500-3100 cm^{-1}). Elemental analysis of the by-product gave the molecular formula $C_{12}H_{12}N_2O$ in agreement with its mass spectrum which showed a parent ion at m/e 200. In addition to the normal proton resonances of the phenyl ring the ^1H n.m.r. spectrum of the by-product exhibited two doublets at δ5.08 and δ5.83 attributable to the coupled OH and CH protons of the exocyclic α-hydroxybenzyl grouping and two further doublets at δ6.98 and δ8.50 for the coupled H-5 and H-6 protons of a 4-substituted pyrimidine ring. Finally the C-4 methyl group appeared as a three-proton singlet at δ2.50 hence confirming the structure of the by-product as the alcohol (298b). The origin of the alcohol (298b) can be explained in terms of participation by water, introduced with the hydrochloric acid, in the breakdown of the triazole ring. Alternatively the alcohol (298b) may be derived by simple hydrolysis of the initially formed chloro-compound (297b). Further evidence to this effect was obtained by the reaction of the unsubstituted triazolo-pyrimidine (296a) with hydrochloric acid under reflux whence the alcohol (298a), for which both analytical and spectroscopic data are in complete concordance with its structure, was obtained in virtually quantitative yield.

That the triazole ring of 1,2,3-triazolo[1,5-a]pyrimidines can be cleaved at room temperature is interesting, though triazole scission at ambient temperature has also been reported[100] for thieno-1,2,3-triazolopyrimidine derivatives. The 1,2,3-triazolo[1,5-a]pyrimidine ring system has been reported[80] to tautomerise to the ring-opened diazoalkyl form at elevated



Scheme 69

temperatures but to exist completely in the triazolopyrimidine form at room temperature. The observation that elevated temperature is not necessary to induce triazole-scission in this ring system therefore precludes the operation of a mechanism (Scheme 68) in which the triazolopyrimidine is thermally isomerised to an open-chain diazoalkyl form followed by protonation to form a diazonium cation and subsequent reaction with a nucleophile to give a triazole cleaved product. It is therefore likely that protonation of the fused triazole species occurs prior to opening of the triazole ring. Westerlund has proposed[100] that, in a related tricyclic triazole system, triazole scission occurs by direct attack of the nucleophile on the intact protonated fused system (Scheme 69). This argument is based upon the fact that in concentrated sulphuric acid the ^1H n.m.r. spectrum of the fused triazole does not display a benzylic type proton. From this observation Westerlund inferred that it is a protonated form of the fused triazole which undergoes nucleophilic attack with subsequent ring opening. However there appear to be two faults in the proposed mechanism. Firstly, the Westerlund mechanism does not take into account the fact that triazole scission is difficult, or even impossible, when the group at C-3 is electron-withdrawing[34,61] whereas an electron-withdrawing group at C-3 would be expected to facilitate triazole scission by the Westerlund mechanism by stabilising the negative charge centred on the exocyclic *C*-atom. Secondly Westerlund has proposed[100] that the initial protonation occurs on the non-triazole nitrogen when it is known[31] that the triazolopyridine ring system can undergo identical triazole ring scission and it is therefore most likely that the initial protonation occurs



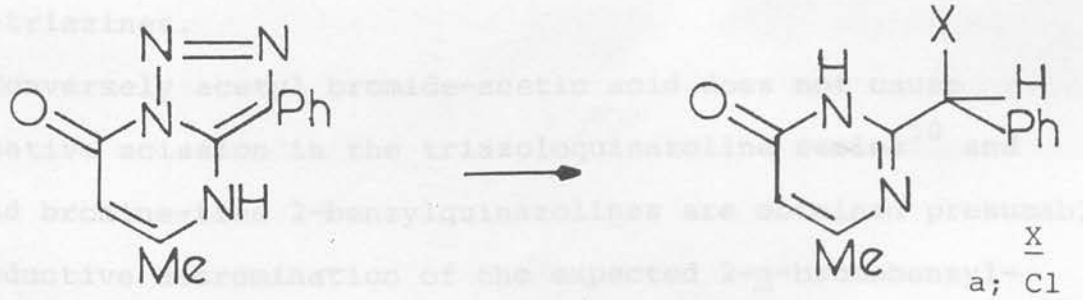
Scheme 70

within the triazole ring. Direct protonation at C-3, as suggested by Novinson[109] can be excluded on the basis that it has been shown[100] that no deuterium incorporation is observed when 3-unsubstituted bridgehead-fused 1,2,3-triazoles are dissolved in deuteriosulphuric acid. Also protonation at the bridgehead nitrogen seems unlikely as this would result in the total loss of aromatic stabilisation in the bicyclic system. It therefore appears that the best candidate for the site of initial protonation in bridgehead-fused 1,2,3-triazoles is N-1 and a plausible mechanism for triazole scission involving such protonation is shown (path a) in Scheme 70. This mechanism can therefore explain the observed absence of deuterium incorporation as well as accounting for the lack of a benzylic type resonance in the ^{1}H n.m.r. spectrum of such triazoles in sulphuric acid. Also implicit in Scheme 70 is the formation of a fully delocalised aromatic ring prior to triazole scission and this will enhance the ease with which the triazole ring can be cleaved. Furthermore the resistance to triazole scission of bridgehead-fused 1,2,3-triazoles bearing an electron-withdrawing group at C-3 can also be accounted for by simple destabilisation of the initial protonated form of the bridgehead-fused 1,2,3-triazole compound and hence inhibition of protonation. Moreover further support for this mechanism (path a) was obtained during attempts to use Lewis acids to catalyse the scission of the triazole ring of 1,2,3-triazolo[1,5-a]pyrimidines (see Section 2.3). In fact Boyer and Wolford proposed[31] a similar mechanism in 1958 but this work seems to have been largely overlooked since then.

It should also be noted that the isolation by Regitz[99]

of a ring-opened diazonium perchlorate during the reaction between a fused triazole derivative and perchloric acid could be taken as evidence for an alternative mechanism to path a in Scheme 70, namely (path b) triazole scission involving ring-opening of the initial protonated bicyclic intermediate to a diazonium salt followed by nucleophilic attack on the latter with displacement of nitrogen to give the observed scission products. However it is difficult to reconcile this alternative mechanism (path b) with the apparent lack of deuterium exchange reported[100] by Westerlund (see before).

1,2,3-Triazolo[1,5-a]pyrimidinones have also been shown[62] (Scheme 71) to take part in acid-promoted triazole ring scission reactions. Thus it is known that the triazolopyrimidinone (299) is transformed into the monocyclic chloro-compound (300a) by the action of acetyl chloride-acetic acid mixtures. On repetition of this reaction it was found that the product isolated had a much lower melting-point than that reported in the literature and as the compound was required for further investigations it was thought prudent to establish its purity. Elemental analysis



(299) (300) X: a; Cl b; OEt

Scheme 71

showed that the pure chlorobenzylpyrimidinone (300a) melted at 175-177°, still well below the literature value of 194°, and it therefore seems likely that the literature value is in error.

When the triazolopyrimidinone (299) was reacted with hydrochloric acid in ethanol the expected chloro-compound (300a) was again obtained but was also accompanied by a by-product whose mass spectrum contained a parent ion at m/e 244. The n.m.r. spectrum of the by-product showed a one-proton singlet at δ5.26 attributable to a benzylic CH group and the triplet-quartet resonances expected for an ethoxy group. The spectrum also contained a three-proton singlet due to a methyl group and a one-proton singlet attributable to H-5 of a pyrimidinone ring. These spectroscopic features are consistent with the ether structure (300b) but despite repeated recrystallization satisfactory analytical data could not be obtained for the compound.

Attention was next turned to the possibility of promoting triazole scission of bridgehead-fused 1,2,3-triazole compounds with accompanying entry of bromide ion as a potential route to 2-bromoalkyl heterocycles. Westerlund has reported the brominative scission of a tricyclic triazole system[100] using hydrobromic acid and it is also known[49] that acetyl bromide-acetic acid effects analogous brominative scission in 1,2,3-triazolo[5,1-c]-1,2,4-triazines.

Conversely acetyl bromide-acetic acid does not cause brominative scission in the triazoloquinazoline series[50] and instead bromine-free 2-benzylquinazolines are obtained presumably via reductive debromination of the expected 2-α-bromobenzyl-quinazoline products.

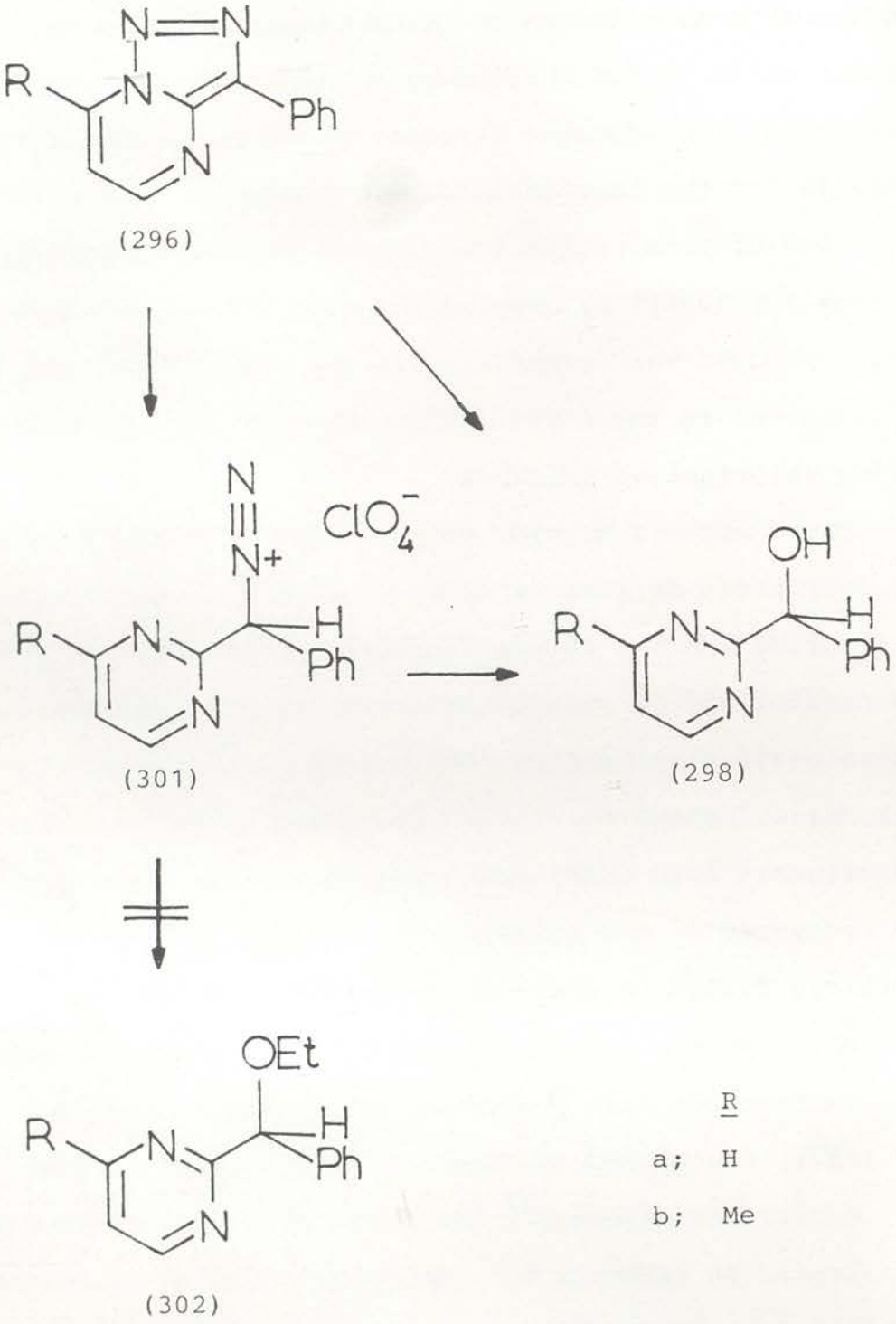
Treatment of 5,7-dimethyl-3-phenyl-1,2,3-triazolo[1,5-a]-pyrimidine [Scheme 65; (287)] with hydrobromic acid in refluxing ethanol for 1 h gave back only starting-material. However increasing both the quantity of the hydrobromic acid and tripling the reaction time did afford a bromine-containing product albeit in poor yield. The mass spectrum of the compound indicated a parent ion of m/e 242 but, in contrast, elemental analysis suggested the molecular formula $C_{15}H_{19}BrN_2O$ (M, 323). These conflicting properties were, however, reconciled when the i.r. spectrum of the substance was found to exhibit a broad absorption band at 2300-2600 cm^{-1} indicative of a hydrohalide salt. Thus the compound was identified as the hydrobromide of the ether [Scheme 65; (288f)] and not as the expected bromobenzylpyrimidine (288c). The formation of the hydrobromide of the ether (288f) is explicable by a route similar to that already proposed (Scheme 65) for the free ether (288f) formed as a by-product on reaction of the triazolopyrimidine (287) with ethanolic hydrochloric acid.

Brominative cleavage of the triazolopyrimidine nucleus was achieved (Scheme 67) when the 5,7-unsubstituted triazolopyrimidine (296a) was reacted with hydrobromic acid at room temperature, the bromo-compound (297c) being obtained in moderate yield along with a small amount of the alcohol (298a) derived by hydrolysis. The bromobenzylpyrimidine (297c) gave the correct elemental analysis but its mass spectrum failed to show the expected parent ion at m/e 249, the highest peak being at m/e 169 corresponding to loss of bromine in the mass spectrometer. The ^1H n.m.r. spectrum of the bromobenzylpyrimidine (297c) exhibited a one-proton singlet at δ6.24 attributable to the benzylic CH proton

and, as well as containing signals due to the phenyl protons, the spectrum also showed in the aromatic region a two proton doublet at δ8.75 for the equivalent H-4 and H-6 protons deshielded by the adjacent nitrogen atoms and a one-proton triplet at δ7.16 for the less deshielded H-5 proton. On attempted extension of brominative scission to the triazolopyrimidinone [Scheme 71; (299)] by heating in ethanolic hydrobromic acid a single product was formed in moderate yield which was shown to be identical to the ether (300b) obtained as a by-product during chlorinative scission.

There appears to have been no report of a bridgehead-fused 1,2,3-triazole derivative being cleaved with accompanying entry of fluoride ion and it was therefore of interest to investigate the possibility of such fluorinative scission in the 1,2,3-triazolo[1,5-a]pyrimidine ring system. On heating the triazolopyrimidine [Scheme 65; (287)] in ethanol with concentrated hydrofluoric acid under mild conditions only the starting material was recovered. The triazolopyrimidinone [Scheme 71; (299)] similarly failed to react on heating with hydrofluoric acid in ethanol. When a greater quantity of hydrofluoric acid was used and the reaction time prolonged the triazolopyrimidine [Scheme 65; (287)] decomposed to produce a multicomponent gum.

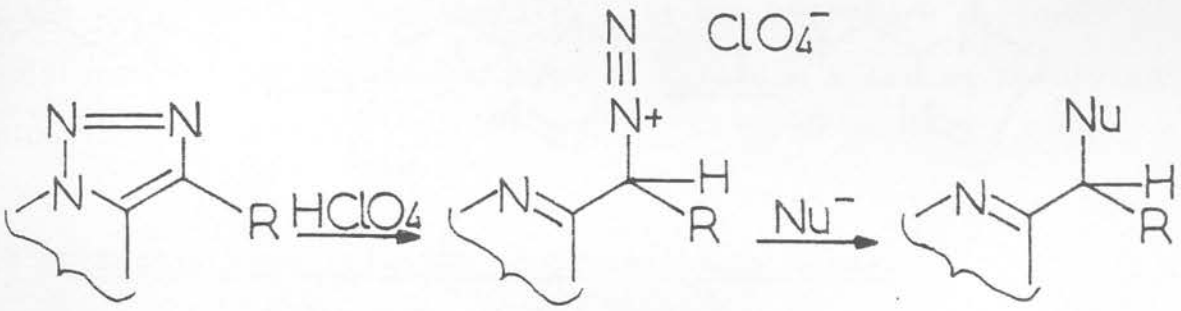
Regitz has reported[99] the formation of a stable diazonium perchlorate on reaction of a bridgehead-fused 1,2,3-triazolopyridine derivative with perchloric acid (see before). Such diazonium cations (Scheme 72) have been proposed as intermediates in triazole scission reactions and it appeared that inclusion of a stronger nucleophile than the very weakly nucleophilic perchlorate ion in the reaction medium might allow the introduction



	R
a;	H
b;	Me

Scheme 73

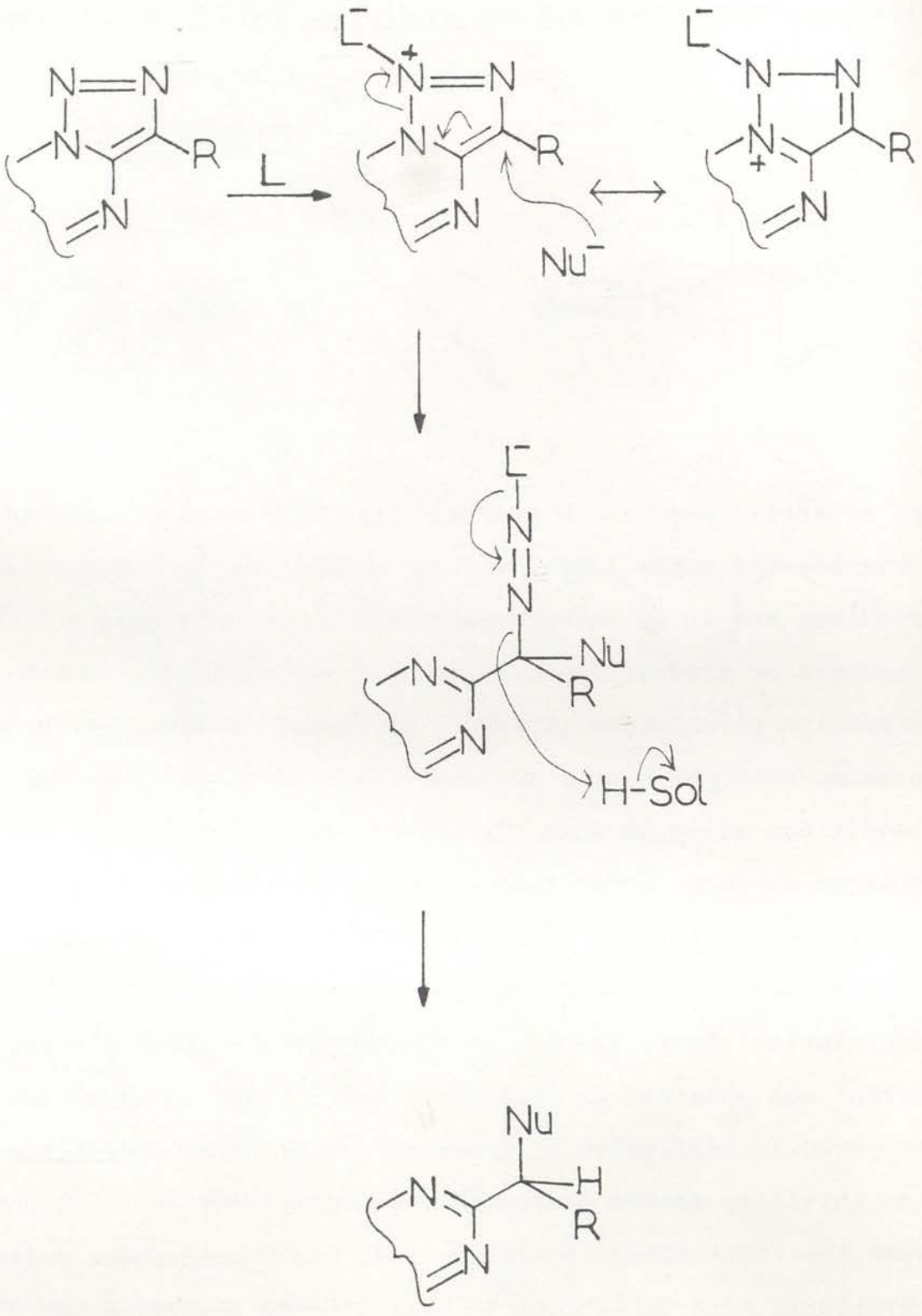
of a variety of nucleophiles via triazole scission in perchloric acid. However when the triazolopyrimidine (296a) was heated



Scheme 72

in ethanolic perchloric acid (Scheme 73), in an attempt to generate the ether (302a) in high yield, only a complex mixture resulted and it is thought that this might have been as a consequence of thermal decomposition of the initially formed diazonium perchlorate (301a). It therefore appeared better to examine such perchloric acid-catalysed scission under ambient conditions although when the triazolopyrimidine (296a) was stirred at room temperature in ethanolic perchloric acid the starting-material was recovered in high yield. On repetition in pure perchloric acid reaction did occur but the diazonium perchlorate (301a) was not observed. Instead the alcohol (298a) was obtained in good yield and the formation of this compound is explicable in terms of a subsequent hydrolysis of the initially formed diazonium perchlorate (301a). In contrast when the triazolopyrimidinone (299) was heated under reflux with perchloric acid in ethanol (Scheme 71) the desired ether (300b) was obtained in fair yield.

The overall picture which emerges from the foregoing studies

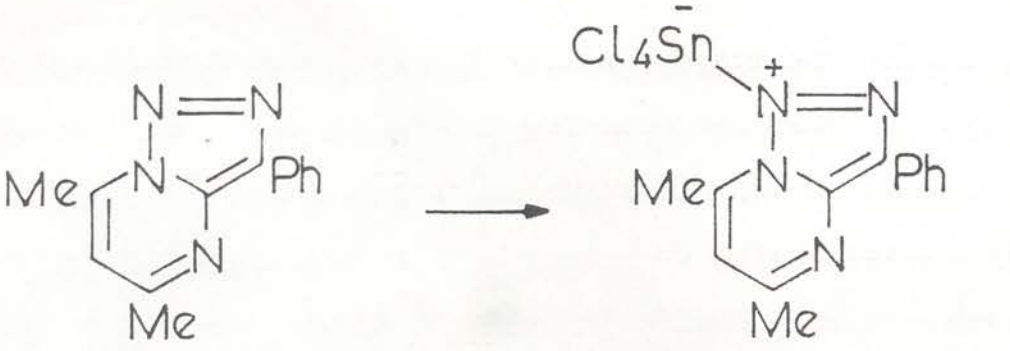


Scheme 74

is that any nucleophile present in the acidic medium can become involved in acid-catalysed triazole scission. With mineral acids attack by the water present always competes with attack by the corresponding nucleophile. It was therefore decided to attempt a more controlled type of triazole scission involving Lewis acids.

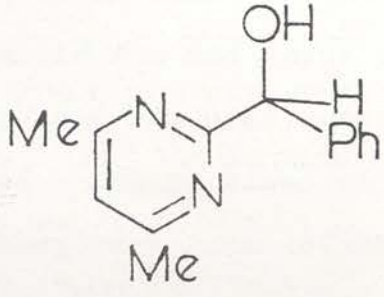
2.3 Triazole Ring Scission Involving Lewis Acids

As the reaction of bridgehead-fused 1,2,3-triazoles with Lewis acids had not hitherto been investigated, it was decided to investigate the behaviour of 1,2,3-triazolo[1,5-a]pyrimidines towards Lewis acids. As already discussed (see page 49 and Scheme 70) acid-catalysed scission of bridgehead-fused 1,2,3-triazoles can be explained in terms of initial protonation at N-1 followed by attack by the nucleophilic counterion on the intact protonated bridgehead-fused triazole ring system. If this mechanism is correct it should be possible to effect triazole scission in a stepwise fashion (Scheme 74) by initial co-ordination with a suitable Lewis acid to give a complex which might be isolable and therefore convertible under controlled conditions by reaction with a range of added nucleophiles into a variety of triazole scission products. It was anticipated (Scheme 74) that under suitable conditions 1,2,3-triazolo-[1,5-a]pyrimidines might react with Lewis acids such as stannic chloride or boron trifluoride to afford complexes capable of reaction with added nucleophiles to provide a new general method for the synthesis of side-chain functionalised pyrimidines. It was also recognised, however, that an incoming nucleophile

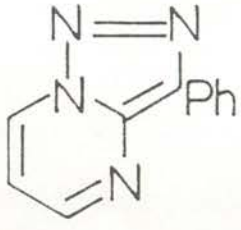


(287)

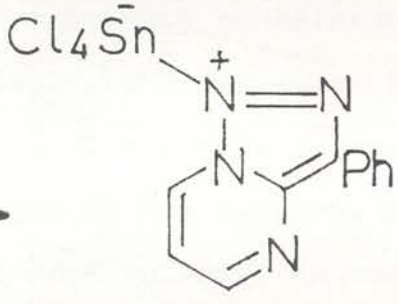
(303)



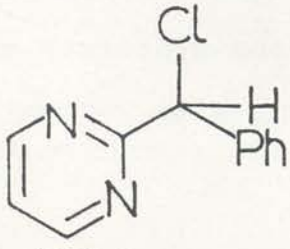
(288e)



(296a)



(304)



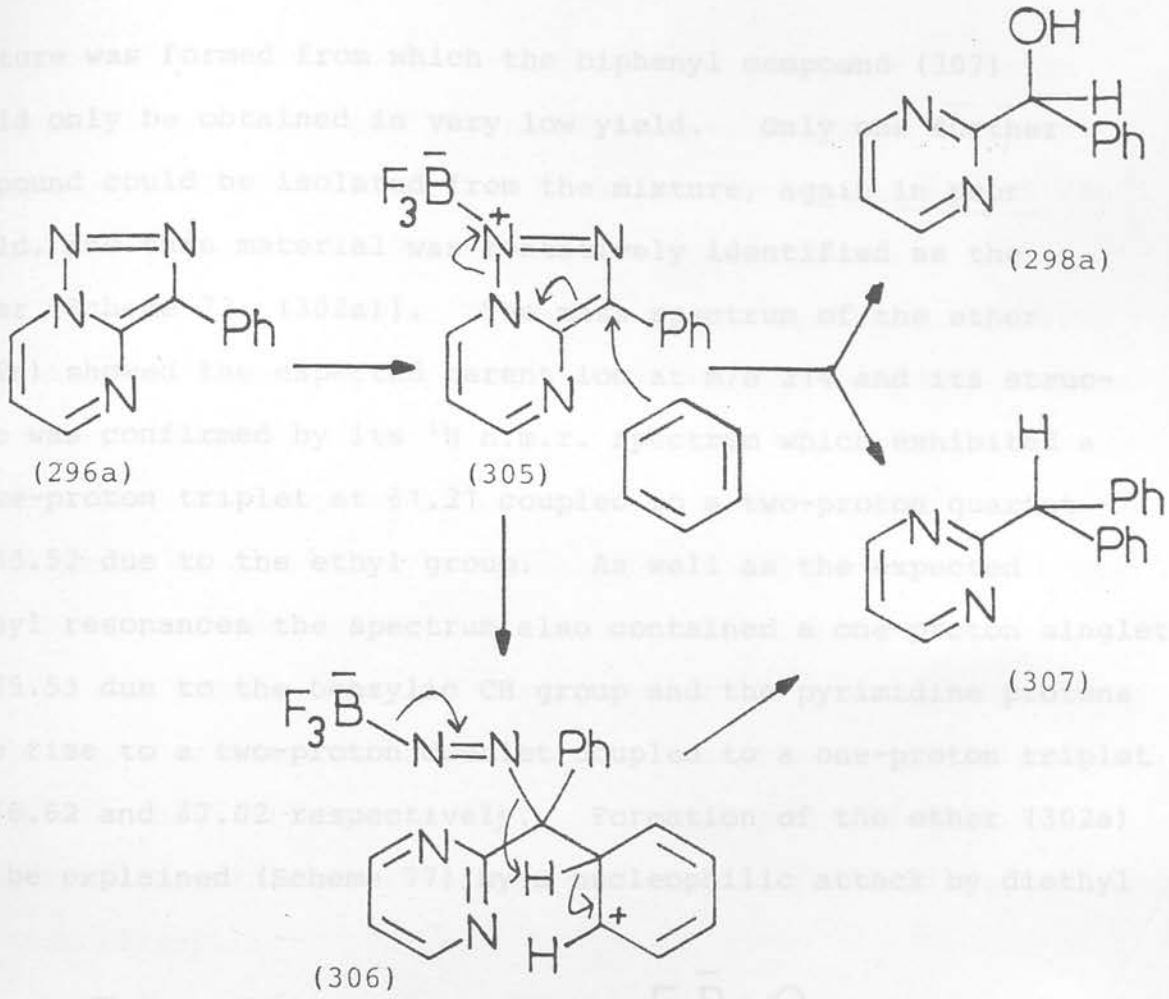
(297a)

Scheme 75

might attack the complex at the Lewis acid moiety with simple reconversion into the starting triazolopyrimidine. In practice both situations were encountered depending on the nature of the nucleophile employed.

Initial attempts to co-ordinate triazolopyrimidines with a Lewis acid (Scheme 75) were made using stannic chloride in an inert solvent. Thus, on stirring in benzene with stannic chloride, the 5,7-dimethyl-3-phenyl-1,2,3-triazolo[1,5-a]-pyrimidine (287) was converted into an inorganic foam. On the assumption that the foam was the stannic chloride-triazolo-pyrimidine complex (303) it was treated with sodium hydroxide in an attempt to form the known alcohol (288e). However the only substance isolated was the starting triazolopyrimidine (287). When the 5,7-unsubstituted triazolopyrimidine (296a) was treated with stannic chloride in benzene (Scheme 75) and stirred at room temperature for 18 h a low melting solid was obtained which was shown to contain inorganic material. Again on the presumption that the complex (304) had been formed the solid was treated with hydrochloric acid in an attempt to form the previously synthesised chloro-compound (297a). However this resulted only in the formation of a multicomponent mixture. In a final attempt to use stannic chloride as a complexing agent the triazolopyrimidinone [Scheme 71; (299)] was treated with this reagent in dioxane at room temperature but subsequent work-up gave only the starting-material in good yield. Because of the failure of stannic chloride to react with 1,2,3-triazolo[1,5-a]pyrimidines to give either characterisable complexes or triazole scission products its study as a reagent for such reactions was abandoned at this stage.

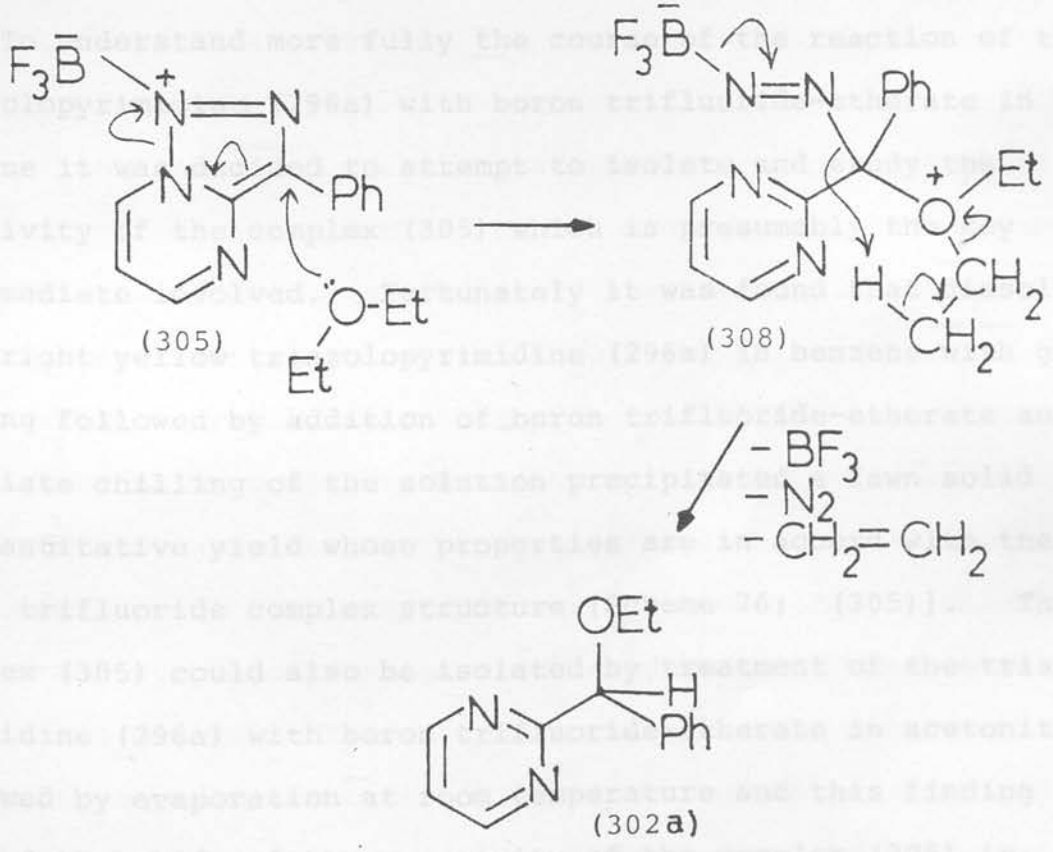
As an alternative to stannic chloride it was decided to investigate boron trifluoride-etherate as a Lewis acid suitable for complexing with 1,2,3-triazolo[1,5-a]pyrimidines and hence for promoting controlled triazole scission. Thus 5,7-dimethyl-3-phenyl-1,2,3-triazolo[1,5-a]pyrimidine [Scheme 65; (287)] was heated under reflux in dioxan with boron trifluoride-etherate to give an inorganic glass work-up of which with sodium hydroxide produced only an intractable tar. Under similar conditions the triazolopyrimidinone [Scheme 71; (299)] gave only a complex mixture. In contrast when 3-phenyl-1,2,3-triazolo[1,5-a]-pyrimidine (296a) was heated under reflux with boron trifluoride in benzene (Scheme 76) a readily separated mixture of two products was obtained. The minor product was identified as the alcohol (298a) which had been obtained previously. The i.r. spectrum of the major product contained no characteristic functional group absorptions and its elemental analysis indicated the molecular formula $C_{17}H_{14}N_2$ in agreement with its mass spectrum which showed a parent ion at m/e 246. The structure of the substance was established by its ^1H n.m.r. spectrum which showed a benzylic proton at δ5.79 and a two-proton doublet at δ8.71 coupled to a one-proton triplet at δ7.10 indicative of a mono-cyclic pyrimidine ring substituted at the 2-position. The remaining resonance was a ten-proton singlet in the aromatic region indicating the presence of two phenyl residues and hence the assignment of the novel triarylmethane structure (307).



Scheme 76

The products (298a) and (307) are thought to be derived from scission of a BF_3-complex of the type (305). Electrophilic attack of the complex (305) on the benzene solvent (Scheme 76) would lead to a zwitterionic intermediate (306) which could then collapse with loss of BF_3 and nitrogen to afford the triarylmethane (307). In anticipation that the alcohol (298a) originated in traces of water present in the reaction medium the reaction of the triazolopyrimidine (296a) with BF_3-etherate was repeated using purified reagents and with careful exclusion of moisture. The expectation that under these conditions complete conversion into the biphenyl compound (307) would result was not however fulfilled. Instead a complex

mixture was formed from which the biphenyl compound (307) could only be obtained in very low yield. Only one further compound could be isolated from the mixture, again in poor yield, and this material was tentatively identified as the ether [Scheme 73; (302a)]. The mass spectrum of the ether (302a) showed the expected parent ion at m/e 214 and its structure was confirmed by its ^{1}H n.m.r. spectrum which exhibited a three-proton triplet at δ1.21 coupled to a two-proton quartet at δ3.52 due to the ethyl group. As well as the expected phenyl resonances the spectrum also contained a one-proton singlet at δ5.53 due to the benzylic CH group and the pyrimidine protons gave rise to a two-proton doublet coupled to a one-proton triplet at δ8.62 and δ7.02 respectively. Formation of the ether (302a) can be explained (Scheme 77) by a nucleophilic attack by diethyl



Scheme 77

ether on the complex (305) with ring-opening of the triazole ring thereby forming the intermediate betaine (308). Collapse of the betaine (308) with loss of BF_3, nitrogen and ethene would thus account for the formation of the ether (302a).

The apparent observation that rigorous exclusion of water caused a decrease in the yield of the biphenyl compound [Scheme 76; (307)] compared with the reaction using unpurified boron trifluoride-etherate suggested that the alcohol (298a) might be a precursor of the triarylmethane product (307). Indeed treatment of the alcohol (298a) with boron trifluoride-etherate in benzene did produce some of the product (307) but only in low yield together with unchanged starting-material. It is probable therefore that the product (307) is formed both directly from the triazolopyrimidine (296a) as well as indirectly from the alcohol (298a).

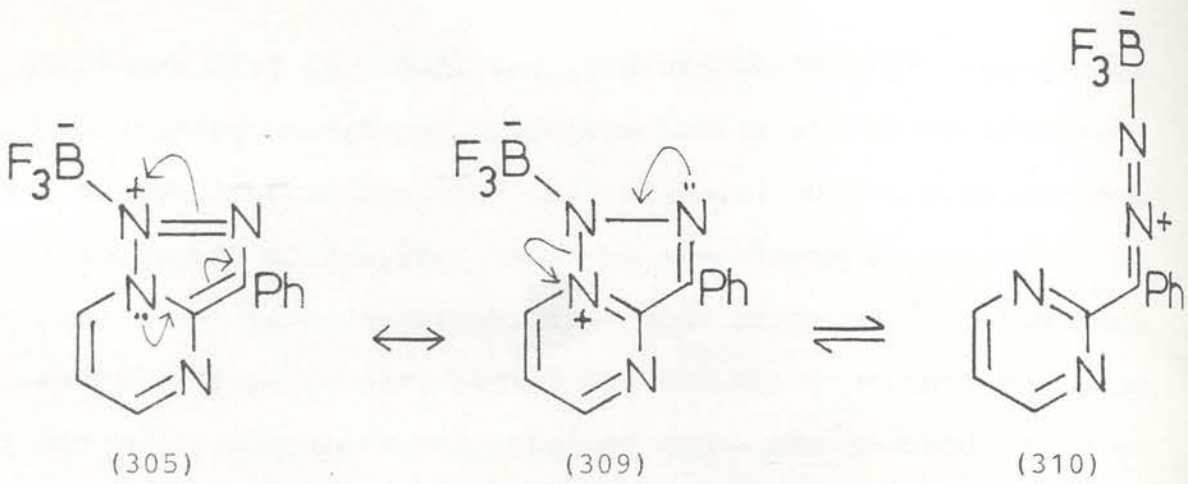
To understand more fully the course of the reaction of the triazolopyrimidine (296a) with boron trifluoride-etherate in benzene it was decided to attempt to isolate and study the reactivity of the complex (305) which is presumably the key intermediate involved. Fortunately it was found that dissolving the bright yellow triazolopyrimidine (296a) in benzene with gentle heating followed by addition of boron trifluoride-etherate and immediate chilling of the solution precipitated a fawn solid in quantitative yield whose properties are in accord with the boron trifluoride complex structure [Scheme 76; (305)]. The complex (305) could also be isolated by treatment of the triazolopyrimidine (296a) with boron trifluoride-etherate in acetonitrile followed by evaporation at room temperature and this finding allowed the study of the reactivity of the complex (305) in

solution.

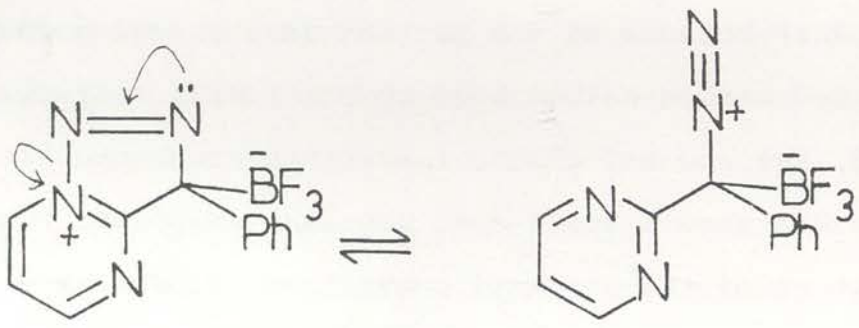
The i.r. spectrum of the solid complex (305) contained various absorptions around 3500 cm^{-1} as well as a band at 2040 cm^{-1} possibly indicating the presence of a ring-opened diazo-species. Also the C=N absorption present at 1600 cm^{-1} in the parent triazolopyrimidine (296a) was shifted to 1630 cm^{-1} in the complex (305) presumably due to the BF_3 moiety whose presence was further indicated by a broad i.r. absorption at 1180-900 cm^{-1}. All attempts to crystallise the complex (305) resulted in removal of the complexed BF_3 with reformation of the parent triazolopyrimidine (296a). Reconversion of the complex (305) into the triazolopyrimidine (296a) also occurred during t.l.c. over silica and on electron impact, the mass spectrum of the complex (305) showing a parent ion corresponding to the triazolo-pyrimidine (296a). Attempted elemental analysis of the complex gave only erratic results and the assignment of the structure and stoichiometry as (305) remains tentative at present. The complex (305) showed no discriminate melting point. Isolation of the BF_3-triazolopyrimidine complex did however allow it to be studied by both ^1H and ^{13}C n.m.r. spectroscopy. To facilitate comparisons, the n.m.r. spectra of both the BF_3-complex and the parent triazolopyrimidine [Scheme 76; (296a)] had to be recorded in the same solvent and deuterionitromethane (CD_3NO_2) was found to be the most appropriate for this purpose. The ^1H and ^{13}C n.m.r. spectra of both compounds were thus obtained in this solvent and completely assigned (an easy task for the proton spectra but one which required numerous low-power proton-decoupling experiments to allow assignment of the carbon spectra). As expected the ^1H n.m.r. spectrum of the parent triazolopyrimidine

contained a trio of double-doublets at δ9.07, 8.77 and 7.22, attributable to the three peripheral pyrimidine protons (H-5, H-6 and H-7). The resonance at δ7.22 can be assigned to H-6 which is not adjacent to a nitrogen atom and is therefore less deshielded. Moreover this double-doublet shows two large coupling constants (J3.9Hz and 7.2Hz) suggesting that it is *ortho* to both of the other two pyrimidine protons. Of the two other double-doublets that at δ9.07 is assigned to H-7, being more deshielded by the electron-deficient bridgehead *N*-atom than the remaining double-doublet at δ8.77 (assigned to H-5) next to N-4. The partial bond fixation of the azaindolizine system would be expected to result in a much greater coupling constant between H-7 and H-6 (7.2Hz) than between H-6 and H-5 (3.9Hz) because of the partial double bond character of the C-6 to C-7 carbon-carbon bond thus allowing confirmation of the H-5, H-6 and H-7 chemical shift assignments. In addition H-7 and H-5 show a small *meta* coupling constant (1.7Hz). The protons of the 3-phenyl substituent appear as a two-proton multiplet at δ8.39 (*ortho*-hydrogens), a two-proton multiplet at δ7.54 (*meta*-hydrogens) and a one-proton multiplet at δ7.41 (*para*-hydrogen). In comparison the ^{1}H n.m.r. spectrum of the triazolopyrimidine-BF_3 complex also exhibited a trio of double-doublets (assigned to H-5, H-6 and H-7 in an identical manner) thus demonstrating that, at least in solution, the complex exists only in the triazole ring-closed form. Moreover, relative to the parent, H-5, H-6 and H-7 are deshielded in accord with the presence of a strongly electron-withdrawing group attached to the bicyclic system.

The ^{13}C n.m.r. spectra of the parent triazolopyrimidine



(305) (309) (310)



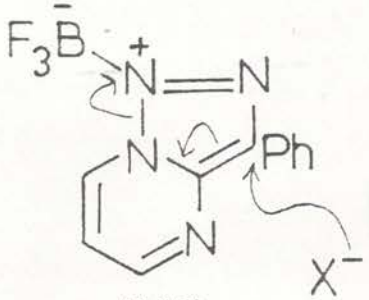
(311) (312)

Scheme 78

(296a) and the derived complex contained nine resonances each, two *ortho* and two *meta* carbons of the phenyl substituent in both cases being equivalent. An immediate implication of the ^{13}C proton-decoupled spectrum of the complex is the appearance of the C-3 carbon as a singlet at δ_C 132.49 which demonstrates that the BF_3 moiety cannot be attached to that carbon atom. Since ^{11}B is a quadrupolar nucleus, had the boron atom been attached to C-3 (or any other *C*-atom) then that carbon atom would have appeared in the proton-decoupled spectrum as a four line resonance. However all of the resonances in the proton-decoupled ^{13}C spectrum of the BF_3-complex were sharp singlets and therefore it is concluded that the boron trifluoride group must be attached to a nitrogen atom. There are two possible structures for the complex (Scheme 78) which would account for its ability, as indicated by its i.r. spectrum, to partially equilibrate with an open-chain diazo tautomeric form, and its chemical reactivity (see later). These are respectively the N(1)-co-ordinated species (305) which can ring-open to the diazonium *N*-betaine (310), and the C(3)-complexed species (311) which can equilibrate with the diazonium *C*-betaine (312) and the structure of both these intermediates is in accord with the known[123-127] behaviour of indolizine and its aza-analogues to be attacked by electrophilic reagents at either the 1- or 3-position. However the latter possibility can definitely be excluded on the basis of the ^1H and ^{13}C n.m.r. absorption of the complex, careful analysis of which strongly supports an *N*-co-ordinated structure but does not allow the unambiguous determination of the precise co-ordination site. Thus N(1) and hence the structure (305) for the complex are most likely when

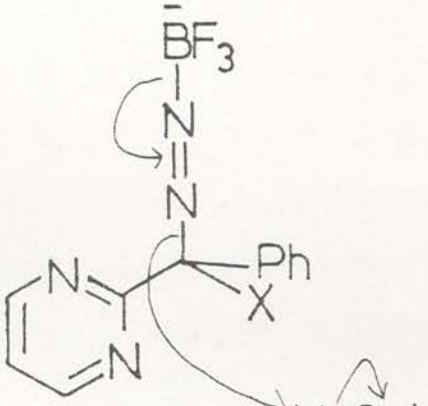
its n.m.r. spectra and chemical reactivity are taken into account. Furthermore a comparison of the relative chemical shifts of the complex (305) and the parent triazolopyrimidine [Scheme 76; (296a)] indicate that C-5, C-6 and C-7 show a marked downfield shift on complexation and this may be explained by the resonance contribution to intermediate (305) by the canonical form (309) in which C-5, C-6 and C-7 have become part of a fully aromatic pyridine ring bearing a positive charge. However although the structure (309) can explain the observed ^{1}H and ^{13}C n.m.r. spectra of the BF_3-complex this evidence does not allow the rigorous structural assignment of the complex except to rule out a *C*-adduct such as (311). The structure (309) can therefore only be tentative in the absence of more rigorous proof based upon X-ray analysis which is precluded by the failure so far of attempts to crystallise the complex. However it is significant that the structure [(305)↔(309)] is akin to that of the protonated intermediate believed to be involved in acid-catalysed scission (see Scheme 70).

The successful cleavage of the triazole ring of the triazolopyrimidine (296a) with excess of boron trifluoride-etherate in benzene prompted an examination of the behaviour of the isolated complex (305) when heated under reflux in benzene. Surprisingly none of the expected triarylmethane derivative [Scheme 76; (307)] was formed but perhaps even more unexpectedly the complex was recovered unchanged in good yield together with only a small amount of the parent triazolo-pyrimidine (296a). This result can be accounted for by the high insolubility of the isolated complex in benzene. An attempt to examine the behaviour of the complex (305) towards



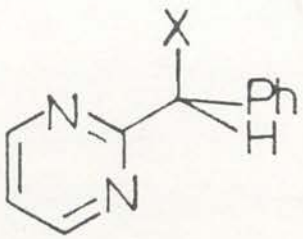
(305)

MX



(313)

	X	MX
a;	Cl	NaCl
b;	Br	NaBr
c;	F	NaF
d;	I	KI
e;	N_3	NaN_3
f;	CN	NaCN
g;	OEt	NaOEt
h;	OAc	NaOAc
i;	$CH(COCH_3)_2$	$NaCH(COCH_3)_2$
j;	SO_2Ph	$NaSO_2Ph$

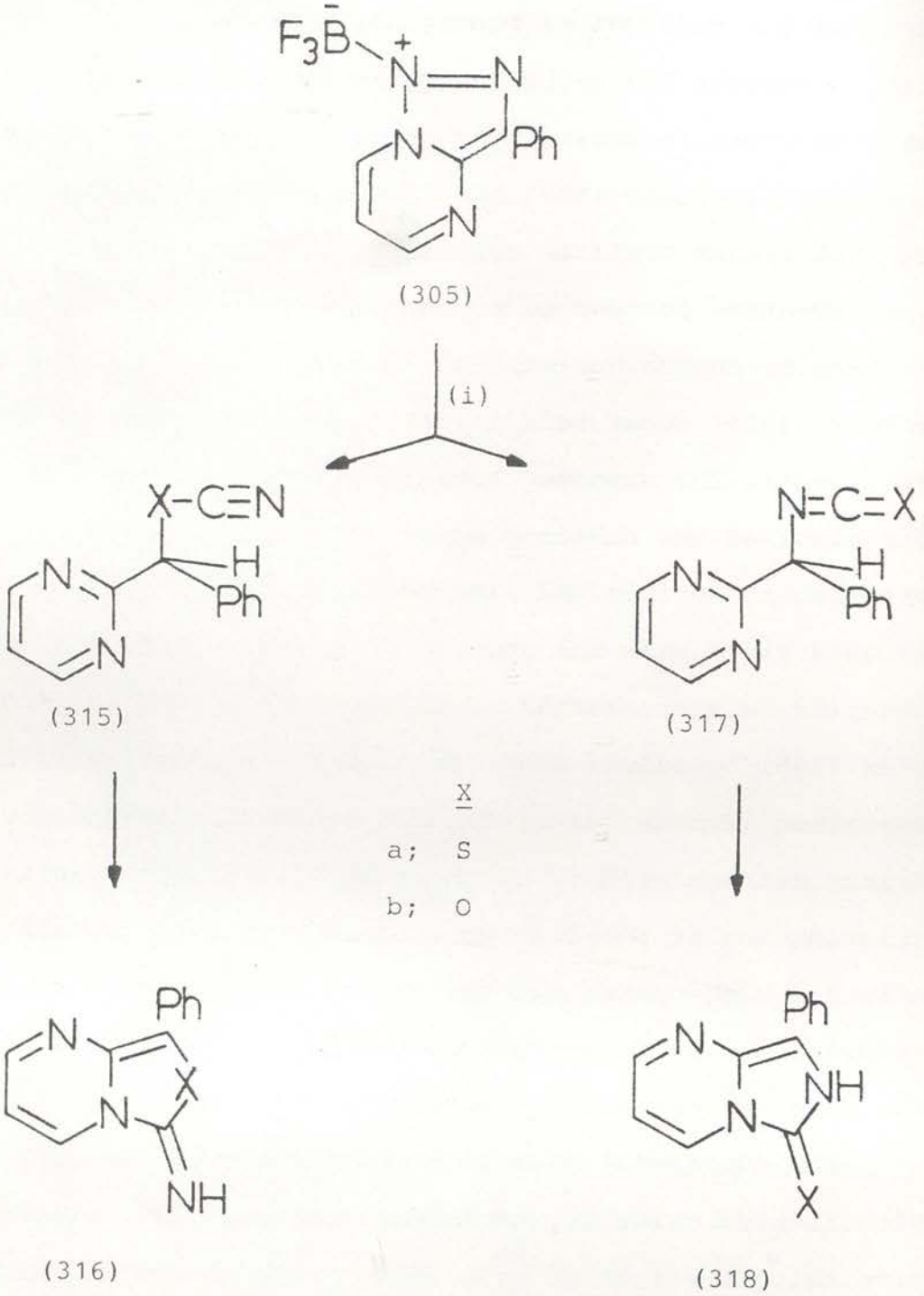


(314)

Scheme 79

dry heating resulted in general decomposition to an intractable tar. However the initial observation that benzene could act as a nucleophile towards the complex (305) in the formation of the triarylmethane (307) did indicate that the triazole ring in this system could be cleaved in a controlled manner and it was therefore decided to attempt such triazole scission with a variety of common nucleophiles (Scheme 79). Heating the complex (305) under reflux with lithium chloride in acetonitrile resulted in the expected scission of the triazole ring with formation of the chloro-compound (314a) in excellent yield and it was also shown that the same compound (314a) could be obtained in good yield when the complex (305) was heated with sodium chloride in acetonitrile. Chlorinative scission of the complex (305) by alkali metal chlorides in acetonitrile can be explained (Scheme 79) as for the formation (Scheme 76) of the triarylmethane product (307). Thus nucleophilic attack by chloride ion at the C(3)-position of the complex (305) would afford a ring-opened species (313a) hydrolysis of which by traces of moisture present in the reaction medium would give the observed end-product (314a).

The successful chlorinative scission of the complex (305) with lithium chloride and sodium chloride, inferring regioselective anionic attack at C(3) rather than at the BF_3 substituent, prompted attempts to extend such reactions to other sodium halides. Accordingly the complex (305) was heated with sodium bromide in acetonitrile (Scheme 79) to give an excellent yield of the expected bromo-compound (314b) which had been synthesised and characterised previously. In contrast heating the complex (305) with sodium fluoride in acetonitrile afforded only a good



(i) NaXCN/heat

Scheme 80

yield of the triazolopyrimidine (296a) none of the hoped for fluoro-compound (314c) being observed. This result indicates that nucleophilic attack by fluoride ion occurs preferentially at boron rather than carbon. Reaction of the complex (305) with iodide ion (Scheme 79), as potassium iodide, produced only a complex mixture from which no identifiable material could be isolated. This result may be a consequence of the anticipated greater instability of the expected iodo-product (314d).

Having demonstrated that the triazole ring of the boron trifluoride-triazolopyrimidine complex (305) could be cleaved at least in some cases by heating with the alkali metal halides to give the corresponding 2-(α-halogenoalkyl)pyrimidines it was decided to investigate the scope of this type of triazole scission as a general route to 2-(α-functionalised alkyl)pyrimidines. Thiocyanate and cyanate ions are pseudohalogens and therefore it was anticipated that the complex (305) might also react with the salts of these anions in a similar fashion to chlorides and bromides. However since the thiocyanate and cyanate ions are ambident nucleophiles the products of such reactions (Scheme 80) could either be the 2-(α-cyanatobenzyl)- and the 2-(α-thiocyanatobenzyl)pyrimidines (315a) or (315b) or the corresponding isocyanate and isothiocyanate derivatives (317a) or (317b). In practice when the complex (305) was heated with sodium thiocyanate in acetonitrile it gave a mixture of products whose i.r. spectrum showed absorption at 2040 cm^{-1} consistent with the presence of the thiocyanatobenzylpyrimidine (315a) or the isothiocyanate derivative (317a). However chromatographic separation of the mixture gave the triazolopyrimidine [Scheme 76; (296a)] and a low yield of a product which lacked i.r.

absorption at 2040 cm^{-1} and was found to be identical to the imidazopyrimidinethione (318a) synthesised later (see Chapter 3). Formation of the triazolopyrimidine (296a) can be explained by preferential reaction of the complex (305) with thiocyanate ion at the BF_3-substituent. Formation of the imidazopyrimidine (318a) can be explained by the spontaneous cyclisation on chromatography of the isothiocyanatobenzylpyrimidine (317a) either present in the original reaction mixture or formed subsequently by rearrangement of the thiocyanate (315a). The presence of the thiocyanate (315a) or the isothiocyanate (317a) in the original reaction mixture is supported by the observed i.r. absorption at 2040 cm^{-1}. Extended heating of the complex (305) with sodium thiocyanate in acetonitrile raised the yield of the imidazopyrimidinethione (318a) to a more respectable 45%. Conversely when the complex (305) was heated with sodium cyanate in acetonitrile none of the imidazopyrimidinone (318b) was observed. Instead only the reformed triazolopyrimidine [Scheme 76; (296a)] was isolated along with multicomponent gums, although the desired imidazopyrimidinone (318b) was later obtained by an alternative route (see Chapter 3).

In order to examine the scope of this mild method for the preparation of various 2-functionalised alkyl pyrimidines the complex (305) was reacted in acetonitrile with a series of alkali metal salts (Scheme 79). However when the complex (305) was heated with either sodium azide, sodium cyanide, sodium ethoxide or sodium acetate the only product isolated was the triazolopyrimidine [Scheme 76; (296a)] thus indicating that these ions react preferentially at the BF_3 moiety. In a similar fashion sodium acetylacetonate and sodium benzenesulphinate also reacted

with the complex (305) selectively at the BF_3 moiety and hence these reactions gave the uncomplexed triazolopyrimidine (296a) as the sole product. Thus while Lewis acid-catalysed scission of the triazole ring of the complex (305) proceeded smoothly for both chloride and bromide ions to give excellent yields of the chloro-compound (314a) and the bromo-compound (314b) the complex (305) reacted preferentially at boron with the majority of other nucleophiles and failed to produce the functionalised pyrimidines (314c-j). This method therefore appears to be limited to the halide ions, chloride and bromide, and thiocyanate ion.

2.4 Experimental

5-Amino-1-benzyl-4-phenyl-1*H*-1,2,3-triazole was prepared (86%) by the method of Hoover and Day[59] and had m.p. 150-152° (lit.,[59] 158°).

5-Amino-4-phenyl-1*H*-1,2,3-triazole was prepared (60-70%) by the method of Hoover and Day[59] and had m.p.124° (lit.,[59] 125°C).

The Preparation of 1,2,3-Triazolo[1,5-a]pyrimidine Derivatives

3-Phenyl-1,2,3-triazolo[1,5-a]pyrimidine (296a) and its 7-methyl and 5,7-dimethyl analogues, (296b) and (287), were prepared as described by Sutherland, Tennant and Vevers[61,122] in respective yields of 95%, 81% and 92%. For comparison with the BF_3-triazolopyrimidine complex (305) the ^1H and ^{13}C n.m.r. spectra of the triazolopyrimidine (296a) were recorded in deuterionitromethane (CD_3NO_2); δ_H (CD_3NO_2) 9.07 (1H, dd, J2 and 7 Hz, H-7), 8.77 (1H, dd, J2 and 4 Hz, H-5), 8.41-8.38 (2H, m, *ortho*-ArH), 7.57-7.51 (2H, m, *meta*-ArH), 7.43-7.39 (1H, m, *para*-ArH) and 7.22 (1H, dd, J4 and 7 Hz, H-6); δ_C (CD_3NO_2) 151.66 (1C, C-5), 139.15 (1C, C-3a), 134.48 (1C, C-3), 131.84 (1C, C-7), 130.20 (1C, C-1'), 127.94 (2C, C-2' and C-6'), 127.14 (1C, C-4'), 125.11 (2C, C-3' and C-5') and 110.48 (1C, C-6).

5-Methyl-3-phenyl-1,2,3-triazolo[1,5-a]pyrimidin-7(4H)-one (299) was prepared (96%) by the method of Sutherland, Tennant and Vevers,[62] with the modification that instead of a catalytic amount of piperidine a three-fold molar equivalent excess was used and had m.p. 215-216° (lit.,[62] 232-234°).

Reactions of 1,2,3-Triazolo[1,5-a]pyrimidine Derivatives with Acetyl Chloride in Glacial Acetic Acid

The triazolopyrimidine derivative (0.002 mol) was heated under reflux in a mixture of acetyl chloride-acetic acid (3:1) (10 ml) for 2.5 h.

(i) The reaction mixture from 3-phenyl-1,2,3-triazolo-[1,5-a]pyrimidine (296a) (0.39 g) was evaporated and co-evaporated with toluene and the residue was subjected to chromatography over silica. Elution with toluene-methylene chloride (40:60) afforded 2-(α-chlorobenzyl)pyrimidine (197a) (0.31 g; 75%) as a colourless oil, b.p.168-170°/3.3 mmHg $\delta(CDCl_3)$ 8.67 (2H, d, J5Hz, H-4 and H-6), 7.8-7.5 (2H, m, ArH), 7.10 (1H, t, J5Hz, H-5) and 6.16 (1H, s, benzylic CH).

Found: C, 64.6; H, 4.4; N, 13.7%; M^+, 206/204.
$C_{11}H_9ClN_2$ requires: C, 64.6; H, 4.4; N, 14.0%; M, 204.5.

(ii) The reaction mixture from 7-methyl-3-phenyl-1,2,3-triazolo[1,5-a]pyrimidine (296b) (0.42 g) was evaporated and co-evaporated with toluene and the resulting red oil (0.46 g) was subjected to preparative t.l.c. in ether over silica to afford 2-(α-chlorobenzyl)-4-methylpyrimidine (297b) (0.32 g; 74%) as a colourless oil, b.p. 186°/6 mmHg, $\delta(CDCl_3)$ 8.60 (1H, d, J5Hz, H-6), 7.7-7.6 (2H, m, ArH), 7.5-7.3 (3H, m, ArH), 7.00 (1H, d, J5Hz, H-5), 6.15 (1H, s, benzylic CH) and 2.50 (3H, s, CH_3).

Found: C, 65.8; H, 5.1; N, 12.8%; M^+,220/218.
$C_{12}H_{11}ClN_2$ requires: C, 65.9; H, 5.1; N, 12.7%; M, 218.5.

(iii) The reaction mixture from 5,7-dimethyl-3-phenyl-

1,2,3-triazolo[1,5-a]pyrimidine (287) (0.45 g) was evaporated and co-evaporated with toluene to give 2-(α-chlorobenzyl)-4,6-dimethylpyrimidine (288b) (0.46 g; 100%) as a fawn solid, m.p. 108-110° (lit.,[61] 112°).

(iv) The reaction mixture from 5-methyl-3-phenyl-1,2,3-triazolo[1,5-a]pyrimidin-7(4H)-one (299) (0.45 g) was evaporated and co-evaporated with toluene to give 2-(α-chlorobenzyl)-6-methylpyrimidin-4(3H)-one (300a), (0.33 g; 70%) as colourless needles, m.p. 175-177° (from ethyl acetate) (lit.,[62] 194°), ν_{max} 3170 and 2730 (NH) and 1680 (CO) cm^{-1}, $\delta(CDCl_3)$ 7.70-7.50 (2H, m, ArH), 7.44-7.20 (3H, m, ArH), 6.23 (1H, s, H-5), 5.87 (1H, s, benzylic CH) and 2.32 (3H, s, CH_3).

Found: M^+, 234.05812

$C_{12}H_{11}ClN_2O$ requires: M, 234.05599

Reactions of 1,2,3-Triazolo[1,5-a]pyrimidine Derivatives with Concentrated Hydrochloric Acid

Method A

The triazolopyrimidine derivative (0.02 mol) was heated under reflux with concentrated hydrochloric acid (10.0 ml) in ethanol (100 ml) for 1 h, and the mixture was worked up as described for the individual reactions below.

(i) The mixture from the triazolopyrimidine (287) (4.5 g) was evaporated to give an amber gum which was treated with water (10.0 ml) to give the solid chlorobenzylpyrimidine (288b) (2.3 g; 50%) m.p.95-98° (lit.,[61] 112°).

The acidic aqueous mother liquor was neutralised with 2M aqueous sodium hydroxide and glacial acetic acid and extracted

with ethyl acetate to give an amber gum (1.44 g) which was shown by t.l.c. in ethyl acetate over alumina to consist of two components. Dry column chromatography of the gum in ether over alumina produced a second crop of the chlorobenzylpyrimidine (288b) (0.09 g; total yield 52%), m.p.103-105° (lit.,[61] 112°) and a minor product characterised as 2-(α-ethoxybenzyl)-4,6-dimethylpyrimidine (288f), (0.31 g; 7%) as colourless prisms, m.p.70-71° (from light petroleum/b.p.40-60°), δ($CDCl_3$) 7.65-7.50 (2H, m, ArH), 7.30-7.20 (3H, m, ArH), 6.80 (1H, s, H-5), 5.52 (1H, s, benzylic CH), 3.58 (2H, q, J7Hz, CH_2), 2.42 (6H, s, $2CH_3$) and 1.25 (3H, t, J7Hz, CH_3).

Found: C, 74.3; H, 7.4; N, 11.7%; M^+, 242.

$C_{15}H_{18}N_2O$ requires: C, 74.4; H, 7.5; N, 11.6%; M, 242.

(ii) The reaction mixture from the triazolopyrimidinone (299) (4.5 g) was evaporated to give a yellow gum which was treated with water (25.0 ml) and extracted with ethyl acetate. Filtration of the three phase mixture gave unchanged starting material (0.25 g; 6%) identical (m.p. and i.r. spectrum) to an authentic sample.

Evaporation of the ethyl acetate extract produced a gummy solid which, when triturated with light petroleum, afforded the chlorobenzylpyrimidinone (300a), (3.1 g; 66%) identical (m.p. and i.r. spectrum) to a sample prepared as described previously.

Evaporation of the light petroleum mother liquor yielded 2-(α-ethoxybenzyl)-6-methylpyrimidin-4(3H)-one (300b), (0.39 g) which was combined with further material obtained by neutralising the acidic aqueous mother liquor with 2M aqueous sodium hydroxide and glacial acetic acid and extracted with methylene

chloride, and crystallised to yield colourless plates (0.14 g; 11%) m.p.103-105° (from ethanol), ν_{max} 3540-3300br and 3200-3120br (NH) and 1670 (CO) cm^{-1}, $\delta(CDCl_3)$ 7.60-7.20 (5H, m, ArH), 6.14 (1H, s, H-5), 5.26 (1H, s, benzylic CH), 3.60 (2H, q, J7Hz, CH_2), 2.24 (3H, s, CH_3) and 1.30 (3H, t, J7Hz, CH_3).

Found: M^+, 244.12307

$C_{14}H_{16}N_2O_2$ requires; M, 244.12117

Method B

A suspension of the triazolopyrimidine derivative (0.02 mol) in concentrated hydrochloric acid (100 ml) was stirred at room temperature for 24 h during which time the solid dissolved to give a colourless solution. The mixture was worked up as described for the individual reactions below.

(i) The mixture from the triazolopyrimidine (296a) (3.9 g) was neutralised with 5M aqueous sodium hydroxide and extracted with methylene chloride to give a pale yellow oil (3.7 g). Flash chromatography of the oil in methylene chloride over silica afforded pure 2-(α-chlorobenzyl)pyrimidine (297a), (3.43 g; 92%) as a colourless oil, identical (i.r. spectrum) to a sample obtained previously.

(ii) The mixture from the triazolopyrimidine (296b) (4.2 g) was neutralised with 5M aqueous sodium hydroxide and glacial acetic acid and extracted with methylene chloride to give a brown oil whose t.l.c. in ethyl acetate over silica showed it to contain two components. Flash chromatography of the oil in ethyl acetate-cyclohexane (67:33) over silica afforded 2-(α-chlorobenzyl)-4-methylpyrimidine (297b), (3.6 g; 83%) as a

colourless oil, identical (i.r. spectrum) to a sample obtained previously.

Further elution gave 2-(α-hydroxybenzyl)-4-methylpyrimidine (298b), (0.24 g; 6%), as cream-coloured plates, m.p. 103-104° (from toluene-light petroleum/b.p.80-100°), ν_{max} 3500-3100br (OH) cm^{-1}, $\delta(CDCl_3)$ 8.50 (1H, d, J5Hz, H-6), 7.55-7.45 (2H, m. ArH), 7.35-7.15 (3H, m, ArH), 6.98 (1H, d, J5Hz, H-5), 5.83 (1H, bd, J5Hz, benzylic CH), 5.08 (1H, bd, J5Hz, OH) and 2.50 (3H, s, CH_3).

Found: C, 71.8; H, 5.3; N, 14.3%; M^+, 200.

$C_{12}H_{12}N_2O$ requires: C, 72.0; H, 6.0; N, 14.0%; M, 200.

Method C

The triazolopyrimidine (296a) (0.39 g, 0.002 mol) in concentrated hydrochloric acid (10.0 ml) was heated under reflux for 2 h during which time the yellow solid dissolved to produce a colourless solution. Dilution of the mixture with water (10.0 ml) followed by neutralisation with 2M aqueous sodium hydroxide and glacial acetic acid afforded 2-(α-hydroxybenzyl)-pyrimidine (298a) which was combined with a second crop obtained by extracting the aqueous mother liquor with methylene chloride and crystallised to give colourless plates (0.38 g; 98%), m.p.103-105° (from light petroleum/b.p.80-100°), ν_{max} 3100-3500 (OH) cm^{-1}, $\delta(CDCl_3)$ 8.64 (2H, d, J4Hz, H-4 and H-6), 7.60-7.20 (5H, m, ArH), 7.11 (1H, t, J4Hz, H-5), 5.86 (1H, s, benzylic CH) and 4.92 (1H, bs, OH).

Found: C, 71.0; H, 5.3; N, 15.0%; M^+, 186.

$C_{11}H_{10}N_2O$ requires: C, 71.3; H, 5.4; N, 15.0%; M, 186.

Reactions of 1,2,3-Triazolo[1,5-a]pyrimidine Derivatives with Concentrated Hydrobromic Acid

Method A

The triazolopyrimidine derivative (0.002 mol) was heated under reflux with 48% aqueous hydrobromic acid (1.0 ml) in ethanol (20 ml) for 1 h, and the mixture was worked up as described for the individual reactions below.

(i) The mixture from the triazolopyrimidine (287) (0.45 g) was evaporated and treated with water (10.0 ml) to give unchanged starting-material (0.23 g; 51%) identical (m.p. and i.r. spectrum) to an authentic sample.

The acidic aqueous mother liquor was neutralised with 2M aqueous sodium hydroxide and glacial acetic acid and extracted with methylene chloride to afford a brown gum (0.11 g). The t.l.c. of the gum in ethyl acetate over silica showed it to be a three component mixture containing starting-material as the main component and therefore it was not further investigated.

(ii) The reaction mixture from the triazolopyrimidinone (299) (0.45 g) was evaporated and treated with water (10.0 ml) to give the unchanged starting-material (299) in quantitative yield, identical (m.p. and i.r. spectrum) to an authentic sample.

Method B

The triazolopyrimidine derivative (0.002 mol) was heated under reflux with 48% aqueous hydrobromic acid (5.0 ml) in ethanol (20 ml) for 3 h and the mixture worked up as described for the individual reactions below.

(i) The mixture from the triazolopyrimidine (287) (0.45 g) was evaporated, treated with water (5.0 ml) and extracted with methylene chloride to give a gum which was triturated with ethyl acetate to afford the hydrobromide of 2-(α-ethoxybenzyl)-4,6-dimethylpyrimidine (288f) (0.14 g; 21%) as pale yellow needles, m.p.169-170° (from ethyl acetate-ethanol), ν_{max} 2300-2600 ($\overset{+}{N}H$) cm^{-1}.

Found: C, 55.8; H, 5.9; N, 8.7%; M^+-HBr, 242.
$C_{15}H_{19}BrN_2O$ requires: C, 55.7; H, 5.8; N, 8.7%; M, 323.

Evaporation of the ethyl acetate mother liquor gave an intractable gum which was not further investigated. Work-up of the aqueous mother liquor gave no further material.

(ii) The mixture from the triazolopyrimidinone (299) (0.45 g) was evaporated and treated with water (10.0 ml) to give the solid 2-(α-ethoxybenzyl)-6-methylpyrimidin-4(3H)-one (300b) which was combined with a second crop obtained by neutralisation of the acidic aqueous mother liquor with 2M aqueous sodium hydroxide and glacial acetic acid and extraction with methylene chloride (total 0.23 g; 63%) identical (m.p. and i.r. spectrum) to a sample obtained previously.

Method C

3-Phenyl-1,2,3-triazolo[1,5-a]pyrimidine (296a), (0.59 g, 0.003 mol) was treated with 48% aqueous hydrobromic acid (7.5 ml) and the mixture was stirred at room temperature for 17 h. The mixture was basified with 5M aqueous sodium hydroxide and extracted with methylene chloride to give a yellow oil (0.57 g) which was flash-chromatographed. Elution with methylene chloride afforded 2-(α-bromobenzyl)pyrimidine (297c) (0.39 g;

52%) as a colourless oil, ($CDCl_3$) 8.75 (2H, d, J5Hz, H-4 and H-6), 7.78-7.66 (2H, m, ArH), 7.42-7.26 (3H, m, ArH), 7.16 (1H, t, J5Hz, H-5) and 6.24 (1H, s, benzylic CH).

Found: C, 52.8; H, 3.7; N, 11.0; M^+, 169 (M-Br). $C_{11}H_9BrN_2$ requires: C, 53.0; H, 3.6; N, 11.2; M, 249.

Elution with methylene chloride-ethyl acetate (20:80) gave unchanged starting-material (0.16 g, 28%) identical (m.p. and i.r. spectrum) to an authentic sample. A small amount of colourless solid (0.02 g; 4%) obtained on elution with ethyl acetate was identified as the alcohol (298a) identical (m.p. and i.r. spectrum) to a sample obtained previously.

When the length of reaction time was increased to 23 h the recovery of starting-material dropped from 28% to 12% but the yield of product (297c) was only increased from 52% to 56%; none of the alcohol (298a) was isolated under these conditions.

The Attempted Reactions of 1,2,3-Triazolo[1,5-a]pyrimidines with Concentrated Hydrofluoric Acid

Method A

The triazolopyrimidine derivative (0.002 mol) was heated under reflux with 48% aqueous hydrofluoric acid (1.0 ml) in ethanol (20.0 ml) for 1 h and the mixture was worked up as described for the individual reactions below.

(i) The mixture from the triazolopyrimidine (287) (0.45 g) was evaporated to give a solid residue which, when treated with water (10.0 ml), gave unchanged starting-material (0.32 g; 72%) identical (m.p. and i.r. spectrum) to an authentic sample.

Work-up of the acidic aqueous mother liquor gave no further material.

(ii) The mixture from the triazolopyrimidinone (299) (0.45 g) was chilled to deposit a colourless crystalline solid which was combined with a further crop obtained by evaporating the ethanolic mother liquor, treatment of the residue with water (3.0 ml) and extraction with methylene chloride, to give the unreacted starting-material (299) (0.43 g; 94%) identical (m.p. and i.r. spectrum) to an authentic sample.

Method B

The triazolopyrimidine (287) (0.45 g, 0.002 mol) was heated under reflux with 48% aqueous hydrofluoric acid (5.0 ml) in ethanol (20.0 ml) and neutralised with 2M sodium hydroxide and glacial acetic acid. Extraction with methylene chloride yielded a dark brown gum (0.43 g) whose t.l.c. in ethyl acetate over alumina showed it to be an inseparable multicomponent mixture, which was not further investigated.

The Attempted Reaction of 3-Phenyl-1,2,3-triazolo[1,5-a]-pyrimidine (296a) with Concentrated Perchloric Acid

(i) A suspension of the triazolopyrimidine (296a) (0.59 g, 0.003 mol) in ethanol (15.0 ml) was treated with 72% aqueous perchloric acid (1.5 ml) and the mixture was stirred at room temperature for 21 h. The undissolved solid was collected to afford unchanged starting-material (296a) more of which was obtained by concentrating the filtrate to remove the ethanol, neutralisation of the acidic aqueous mother liquor with 2M

aqueous sodium hydroxide and glacial acetic acid and extraction with methylene chloride (total 0.59 g; 100%) and identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

(ii) A suspension of the triazolopyrimidine (296a) (0.59 g, 0.003 mol) in 72% aqueous perchloric acid (15.0 ml) was stirred at room temperature for 18 h during which time the yellow solid completely dissolved. Basification of the reaction mixture with 5M aqueous sodium hydroxide and extraction with methylene chloride gave a pale brown solid (0.37 g) which was flash-chromatographed in ethyl acetate over silica to give the alcohol (298a), (0.32 g; 57%) identical (m.p. and i.r. spectrum) to a sample obtained previously. Work-up of the basic aqueous mother liquor gave no further material.

The Attempted Reaction of 5,7-Dimethyl-3-phenyl-1,2,3-triazolo[1,5-a]pyrimidine (287) with Concentrated Perchloric Acid

The triazolopyrimidine (287) (0.49 g, 0.002 mol) was dissolved in ethanol (20.0 ml), treated with 72% aqueous perchloric acid (1.0 ml) and the mixture heated under reflux for 1 h. The mixture was evaporated, treated with water (5.0 ml), neutralised with 2M aqueous sodium hydroxide and glacial acetic acid and extracted with methylene chloride to give a brown gum (0.42 g) whose t.l.c. in ethyl acetate over alumina showed it to be a multicomponent mixture which was not investigated further.

The Attempted Reaction of 5-Methyl-3-phenyl-1,2,3-triazolo-[1,5-a]pyrimidin-7(4H)-one (299) with Concentrated Perchloric Acid

The triazolopyrimidinone (299)(0.90 g, 0.004 mol) was dissolved in ethanol (60.0 ml), treated with 72% aqueous perchloric acid (2.0 ml) and the mixture heated under reflux for 1 h. The mixture was evaporated, treated with water (10.0 ml), neutralised with 2M aqueous sodium hydroxide and glacial acetic acid and extracted with methylene chloride to afford 2-(α-ethoxybenzyl)-6-methylpyrimidin-4(3H)-one (300b), (0.40 g; 41%) identical (m.p. and i.r. spectrum) to a sample obtained previously.

The Attempted Reaction of 1,2,3-Triazolo[1,5-a]pyrimidines with Stannic Chloride

(i) A solution of triazolopyrimidine (296a) (0.59 g, 0.003 mol) in dry benzene (15.0 ml) was treated in one portion with stannic chloride (5.0 ml) and the mixture was stirred at room temperature for 18 h during which time the initially yellow solution turned colourless. The mixture was treated with ice (50.0 g) which on melting produced a three phase system. Filtration removed a pale yellow low-melting solid (1.17 g) which was shown to contain inorganic material (i.r. spectrum and residue on burning). Treatment of the solid with 2M aqueous hydrochloric acid and extraction with methylene chloride gave a pink gum (0.38 g) whose t.l.c. in ethyl acetate over silica showed it to be an inseparable multicomponent mixture which was not further investigated.

Evaporation of the organic layer gave no material and likewise work-up of the acidic aqueous layer gave no material.

(ii) A solution of the triazolopyrimidine (287) (0.45 g, 0.002 mol) in dry benzene (10.0 ml) was treated in one portion with stannic chloride (0.5 ml) and the mixture was stirred magnetically at room temperature for 1 h during which time a gas was evolved and a gum was deposited. The mixture was treated with ice (20.0 g), benzene (20.0 ml) and ethyl acetate (20.0 ml) and the organic phase was evaporated to give a yellow foam (0.67 g) shown (i.r. spectrum and residue on burning) to contain inorganic material. Treatment of the foam with 2M aqueous sodium hydroxide and extraction with methylene chloride afforded unchanged starting-material (0.21 g; 46%) identical (m.p. and i.r. spectrum) to an authentic sample. Work-up of the basic aqueous mother liquor produced no further material.

(iii) A solution of the triazolopyrimidine (299), (0.27 g, 0.0012 mol) in dry dioxane (6.0 ml) was treated in one portion with stannic chloride (0.3 ml) and the mixture was stirred at room temperature for 1 h. The mixture was treated with ice (50.0 g) and the deposited solid was combined with a second crop obtained by extracting the aqueous dioxane mother liquor with methylene chloride to give unreacted starting-material (296a) (total 0.23 g; 85%) identical (m.p. and i.r. spectrum) to an authentic sample.

Reactions of 1,2,3-Triazolo[1,5-a]pyrimidines with Boron Trifluoride Etherate

Method A

The triazolopyrimidine derivative (0.002 mol) was heated under reflux with boron trifluoride etherate (5.0 ml) in dry

dioxane (15.0 ml) for 0.5 h and the mixture was worked up as described for the individual reactions below.

(i) The reaction mixture from the triazolopyrimidine (287) (0.45 g) was evaporated, treated with water (10.0 ml) and extracted with methylene chloride to produce a glass-like gum (0.67 g) shown (residue on burning) to contain inorganic material. Treatment of the gum with 2M aqueous sodium hydroxide and extraction with methylene chloride gave a black intractable tar (0.28 g) which was not investigated further. Work-up of the basic aqueous mother liquor gave no further material.

(ii) The reaction mixture from the triazolopyrimidine (299) (0.45 g) was evaporated, treated with water (10.0 ml) and extracted with methylene chloride to give a brown gum (0.54 g) which was shown by t.l.c. in ethyl acetate over alumina to be an inseparable multicomponent mixture and therefore was not further investigated.

Method B

The triazolopyrimidine (296a) (0.59 g, 0.003 mol) was heated under reflux with boron trifluoride etherate (5.0 ml) in dry benzene (20.0 ml) for 3 h. The mixture was evaporated, treated with water (20.0 ml), neutralised with 2M aqueous sodium hydroxide and glacial acetic acid and extracted with methylene chloride to give a red oil (0.57 g) whose t.l.c. in ethyl acetate over silica showed it to contain two components which were separated by flash chromatography. Elution with methylene chloride-ethyl acetate (50:50) gave diphenylpyrimid-2-ylmethane (307) (0.31 g; 42%), as colourless needles, m.p. 78-79° (from light petroleum), $\delta(CDCl_3)$ 8.71 (2H, d, J5Hz,

H-4 and H-6), 7.29 (10H, s, ArH), 7.10 (1H, t, J5Hz, H-5) and 5.79 (1H, s, benzylic CH).

Found: C, 82.7; H, 5.7; N, 11.7%; M^+, 246.

$C_{17}H_{14}N_2$ requires: C, 82.9; H, 5.7; N, 11.4%; M, 246.

Further elution with ethyl acetate gave the alcohol (298a), (0.20 g; 36%) identical (m.p. and i.r. spectrum) to a sample obtained previously.

Method C

Repetition of the reaction as in B before, but with the rigorous exclusion of moisture and using freshly distilled boron trifluoride etherate gave a brown gum (0.55 g) whose t.l.c. in ethyl acetate over silica showed it to be a multicomponent mixture. Attempted separation of this mixture was only partially successful. Elution with methylene chloride afforded the diphenylpyrimidylmethane (307) (0.03 g; 4%) identical (m.p. and i.r. spectrum) to a sample obtained in B before.

Further elution with ethyl acetate gave 2-(α-ethoxybenzyl)-pyrimidine (302a), (0.06 g; 9%), $\delta(CDCl_3)$ 8.62 (2H, d, J5Hz, H-4 and H-6), 7.55-7.14 (5H, m, ArH), 7.02 (1H, t, J5Hz), 5.53 (1H, s, benzylic CH), 3.52 (2H, q, J7Hz, CH_2) and 1.21 (3H, t, J5Hz, CH_3), m/e 214 (M, 214).

Method D

The triazolopyrimidine (296a) (3.92 g, 0.02 mol) was dissolved in dry benzene (110 ml) with gentle heating and treated in one portion with freshly distilled boron trifluoride etherate (14.20 g, 0.10 mol). Cooling in ice gave the triazolopyrimidine-boron trifluoride etherate complex (305) (5.26 g; 100%) which

showed no discriminate melting point, ν_{max} 2040 (N≡N) and 1630 (C=N) cm^{-1}, δ_H (CD_3NO_2) 9.36-9.34 (1H, dd, J2 and 7Hz, H-7Hz), 9.19-9.21 (1H, dd, J2 and 4Hz, H-5), 8.37-8.35 (2H, m, ArH), 7.88-7.85 (1H, dd, J4 and 7Hz, H-6) and 7.75-7.69 (3H, m, ArH); δ_C (CD_3NO_2) 155.81 (d, C-5), 138.82 (s, C-3a), 132.77 (d, C-7), 132.49 (s, C-3), 131.11 (d, C-4'), 128.89 (d, C-2' and C-6'), 126.77 (d, C-3' and C-5'), 122.46 (s, C-1') and 117.34 (d, C-6), m/e 196 (M^+-BF_3).

Method E

The triazolopyrimidine (296a) (0.59 g, 0.003 mol) was dissolved in dry acetonitrile (25.0 ml), treated in one portion with freshly distilled boron trifluoride etherate (0.43 g, 0.003 mol) and the solution was left at room temperature for 15 min. The solvent was evaporated under reduced pressure (oil pump) at room temperature and the yellow glassy residue was triturated with ether to give a pale yellow solid (0.57 g) whose i.r. spectrum showed it to be a mixture of unchanged starting material and product. The solid was redissolved in dry acetonitrile (10.0 ml), treated with a further portion of boron trifluoride etherate (0.43 g, 0.003 mol) and again left at room temperature for 15 min. Evaporation of the solvent under reduced pressure (oil pump) at room temperature gave a fawn residue which was triturated with ether to afford the triazolopyrimidine-boron trifluoride complex (305), (0.64 g; 84%) identical (i.r. spectrum) to a sample obtained previously.

The Reaction of 2-(α-Hydroxybenzyl)pyrimidine (298a) with Boron Trifluoride Etherate

A solution of the alcohol (298a), (0.37 g, 0.002 mol) in

dry benzene (20.0 ml) was treated in one portion with boron trifluoride etherate (5.0 ml) and the mixture was heated under reflux for 3 h. The mixture was evaporated, treated with water (20.0 ml) and neutralised with 2M aqueous sodium hydroxide and glacial acetic acid. Extraction with methylene chloride gave a red oil (0.25 g) whose t.l.c. in ethyl acetate over silica showed it to be a two component mixture.

Flash chromatography of the oil in ethyl acetate over silica yielded the diphenylpyrimidylmethane (307) (0.10 g; 19%) as the minor component, identical (m.p. and i.r. spectrum) to a sample obtained previously, and as the major component unchanged starting material (298a) (0.15 g, 39%) identical (m.p. and i.r. spectrum) to an authentic sample.

The Thermal Behaviour of the Triazolopyrimidine Boron Trifluoride Complex (305)

(i) A suspension of the complex (305) (0.53 g, 0.002 mol) in dry benzene (10.0 ml) was heated under reflux for 3 h. Hot-filtration of the mixture afforded the unchanged starting-material (305) (0.43 g; 82%) identical (m.p. and i.r. spectrum) to an authentic sample.

(ii) The complex (305), (0.53 g, 0.002 mol) was heated in a cold-finger apparatus under reduced pressure (water pump) at 160° (oil bath) for 30 min. Decomposition occurred leaving a black intractable tar which showed no separable components on t.l.c. in ethanol over silica and therefore was not further investigated.

Reactions of the Triazolopyrimidine-Boron Trifluoride Etherate Complex (305) with Alkali Metal Halides and Related Salts

Method A

The complex (305) (0.53 g, 0.002 mol) was dissolved in dry acetonitrile (10.0 ml), treated with the appropriate salt (0.008 mol) and the mixture heated under reflux for 3 h. The mixture was cooled, filtered to remove excess salt and the filtrate was evaporated to give a residue which was redissolved in methylene chloride, filtered to remove inorganic material and evaporated to give the product.

(i) lithium chloride

The red oil from the methylene chloride extract was flash chromatographed in methylene chloride over silica to yield the pure 2-(α-chlorobenzyl)pyrimidine (314a) as a colourless oil (0.37 g; 91%) identical (i.r. spectrum) to a sample obtained previously.

(ii) sodium chloride

Evaporation of the methylene chloride extract gave the chloro-compound (314a) (71%), identical (i.r. spectrum) to a sample obtained previously.

(iii) sodium bromide

Evaporation of the methylene chloride extract gave a dark oil (0.44 g) which was purified by flash chromatography in methylene chloride over silica to give 2-(α-bromobenzyl)-pyrimidine (314b) as a colourless oil (0.39 g; 78%) identical (i.r. spectrum) to a sample obtained previously.

(iv) sodium fluoride

Evaporation of the methylene chloride extract gave the triazolopyrimidine (296a), (0.35 g; 88%), identical (m.p. and i.r. spectrum) to an authentic sample.

(v) potassium iodide

Evaporation of the methylene chloride extract yielded a dark brown foam (0.54 g) whose t.l.c. in ethyl acetate over silica showed it to be an inseparable multicomponent mixture which was therefore not further investigated.

(vi) sodium azide

Evaporation of the methylene chloride extract afforded the triazolopyrimidine (296a) in quantitative yield, identical (m.p. and i.r. spectrum) to an authentic sample.

(vii) sodium cyanide

Evaporation of the methylene chloride extract afforded the triazolopyrimidine (296a) (0.30 g; 76%) identical (m.p. and i.r. spectrum) to an authentic sample.

(viii) sodium acetate

Evaporation of the methylene chloride extract gave the triazolopyrimidine (296a) (0.28 g; 72%) identical (m.p. and i.r. spectrum) to an authentic sample.

(ix) sodium acetylacetonate

Evaporation of the methylene chloride extract gave the triazolopyrimidine (296a), (0.28 g; 72%) identical (m.p. and i.r. spectrum) to an authentic sample.

(x) sodium benzenesulphinate

Evaporation of the methylene chloride extract gave an oily yellow solid (0.48 g), which was flash chromatographed in methylene chloride over silica to afford the triazolopyrimidine (296a) (0.21 g; 54%) identical (m.p. and i.r. spectrum) to an authentic sample.

Method B

(i) The complex (305) (0.53 g, 0.002 mol) was dissolved in dry acetonitrile (10.0 ml), treated in one portion with solid sodium thiocyanate (0.65 g, 0.008 mol) and the mixture was heated under reflux for 1.5 h. Evaporation of the mixture gave a crimson residue which was treated with water (10.0 ml) and filtered to give a red solid (0.38 g), ν_{max} 2040 cm^{-1}, whose t.l.c. in ethyl acetate over silica showed it to be a two component mixture.

Flash chromatography of the solid mixture in methylene chloride over silica gave as the first fraction the triazolopyrimidine (296a) as a yellow solid (0.09 g; 24%) identical (m.p. and i.r. spectrum) to an authentic sample.

Further elution with methylene chloride gave the imidazopyrimidinethione (318a) identical (m.p. and i.r. spectrum) to a sample obtained later.

Work-up of the acidic aqueous mother liquor gave no further material.

(ii) Repetition of the above reaction with extended heating (4 h) increased the yield of the imidazopyrimidine-thione (318a) to 45%.

Method C

The complex (305) (0.53 g, 0.002 mol) was dissolved in dry acetonitrile (10.0 ml) treated in one portion with solid potassium cyanate and heated under reflux for 6 h. The filtrate was evaporated to give an orange solid (0.42 g) whose t.l.c. in ethyl acetate over silica showed it to be a multicomponent mixture containing the triazolopyrimidine (296a) as the main component. The mixture was separated by flash chromatography over silica.

Elution with methylene chloride gave the triazolopyrimidine (296a) (0.17 g; 43%) identical (m.p. and i.r. spectrum) to an authentic sample.

Further elution with ethyl acetate and then ethanol gave two crops of yellow gum (0.06 g and 0.04 g respectively) both of which were shown by t.l.c. in ethanol over silica to be multicomponent mixtures and therefore were not investigated further.

Method D

The complex (305) (0.53 g, 0.002 mol) was dissolved in dry acetonitrile (10.0 ml) treated in one portion with solid sodium ethoxide (0.54 g, 0.008 mol) and the mixture was heated under reflux for 3 h during which time it turned deep crimson in colour. Evaporation of the mixture gave a brown solid which was treated with water (10.0 ml) and the solution neutralised with 2M aqueous hydrochloric acid and solid sodium acetate. Attempted extraction with methylene chloride gave a three phase system which was filtered and the solid combined with a second crop obtained by evaporating the methylene chloride layer to

give the triazolopyrimidine (296a) (total 0.35 g; 88%) identical (m.p. and i.r. spectrum) to an authentic sample.

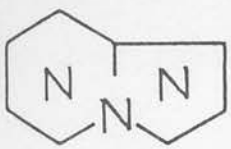
Chapter 3

New Syntheses of Imidazo[1,5-a]pyrimidine Derivatives

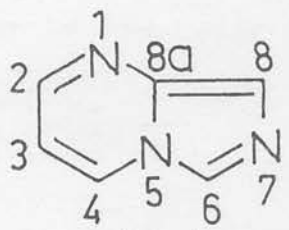
New Syntheses of Imidazo[1,5-a]pyrimidine Derivatives

3.1 Introduction

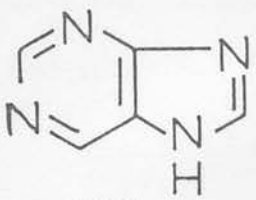
Azaindolizines (320) in general have received much attention recently[128,129] and the literature contains numerous references[130-138] to such ring systems containing a 1,5-fused imidazole ring. In contrast derivatives of the imidazo[1,5-a]-pyrimidine ring system (321) have only rarely been reported. This is surprising in view of the close structural similarity of the imidazo[1,5-a]pyrimidine ring system (321) to purine (322) and hence the possible biological activity, as scrambled purines, of derivatives of the former ring system.



(320)

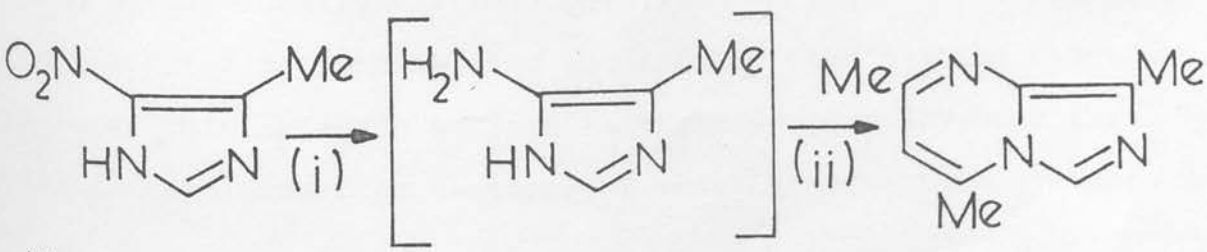


(321)



(322)

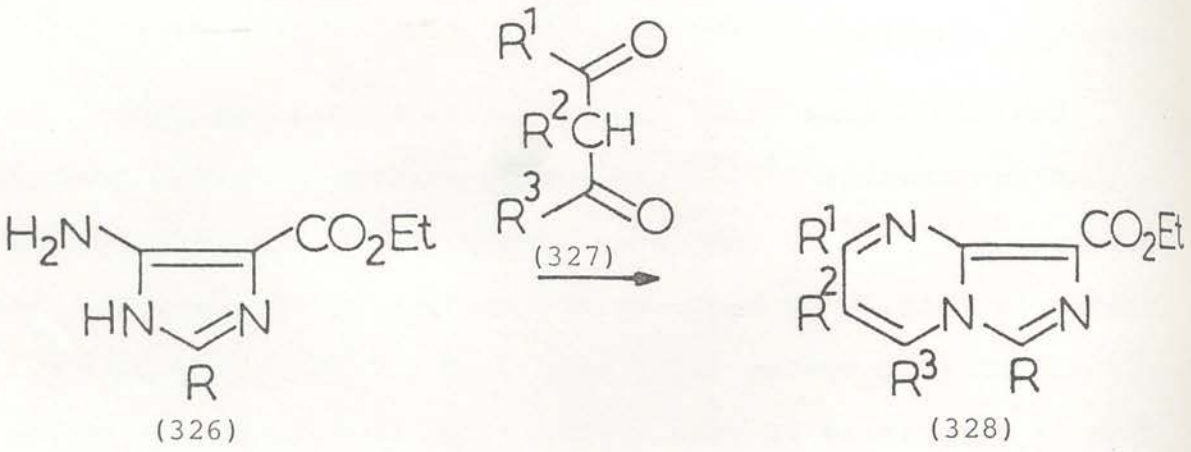
The first synthesis of an imidazo[1,5-a]pyrimidine derivative (Scheme 81) was reported as early as 1939 when Ochai and Sibata[139] showed that 5-amino-4-methylimidazole (324) [formed *in situ* by the reduction of 4-methyl-5-nitroimidazole (323)] condensed with acetylacetone to give the 2,4,8-trimethyl-imidazo[1,5-a]pyrimidine (325). After this isolated report the



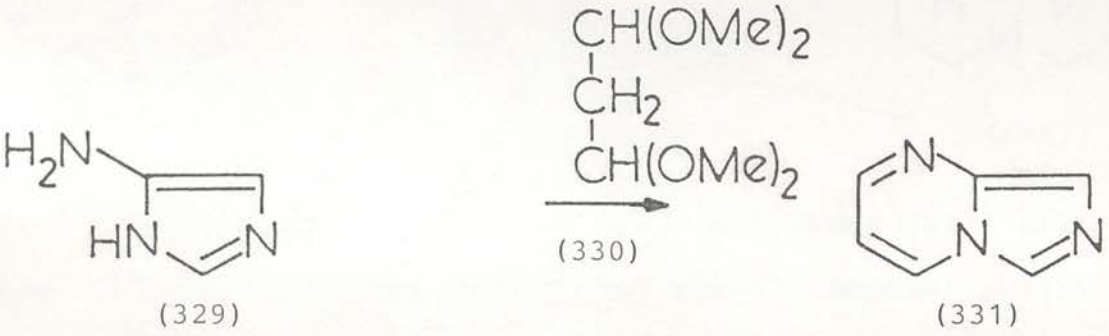
(i) [H] (323) (324) (325)

(ii) $MeCOCH_2COMe$

Scheme 81

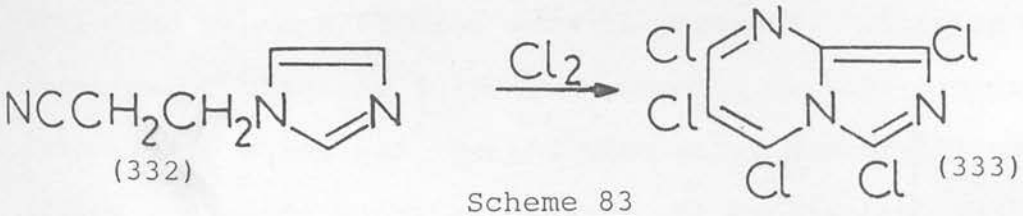


(R=H, Me or Ph; R^1, R^2, R^3=H or Me)



Scheme 82

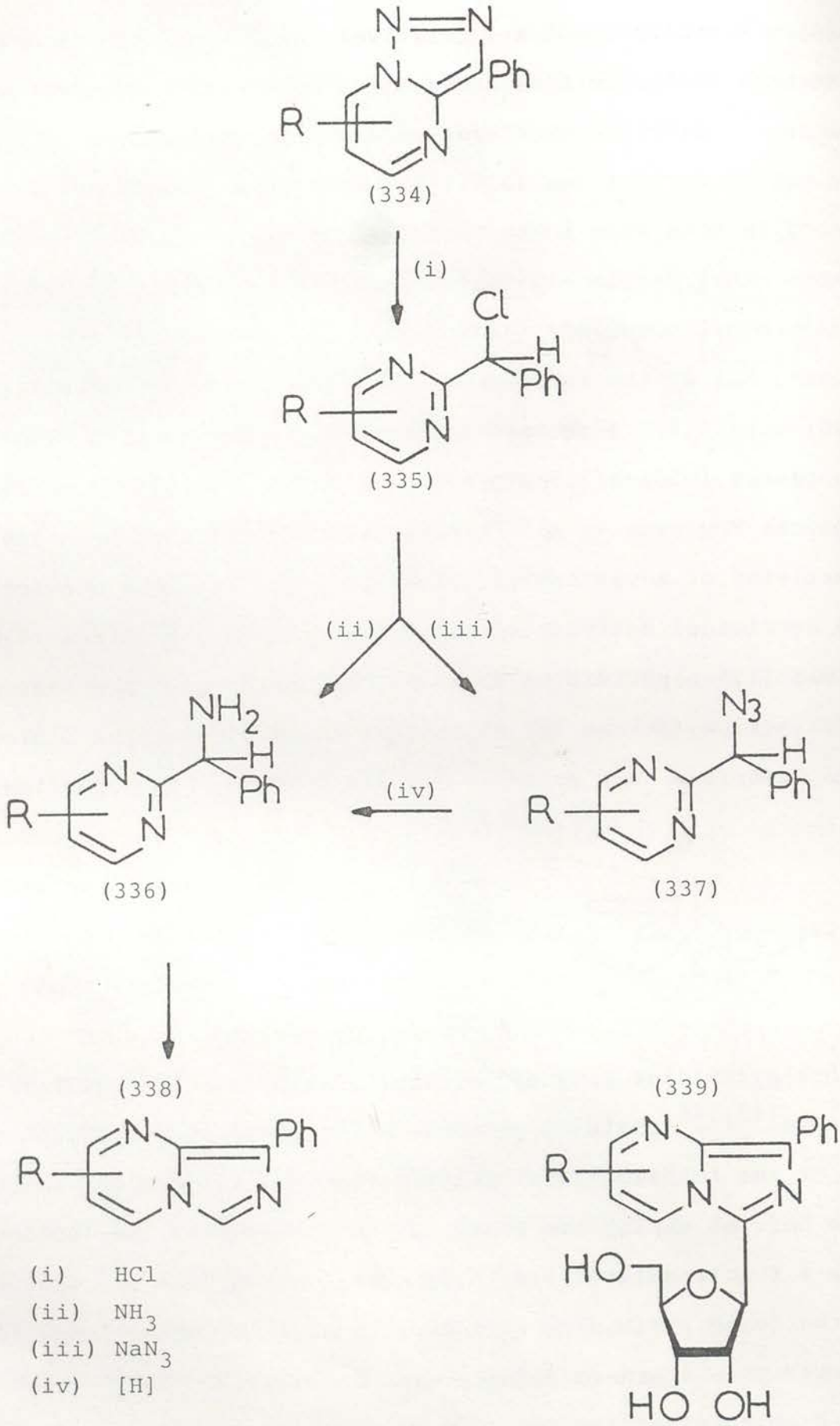
imidazo[1,5-a]pyrimidine ring system did not attract further attention until the early seventies when Guerret and his co-workers[140] reported syntheses of a series of imidazo[1,5-a]-pyrimidine derivatives (328) (Scheme 82). The synthetic method in this work again involved the condensation of relatively stable ethyl 5-amino-1H-imidazole-4-carboxylates (326) with β-dicarbonyl compounds (327). The analogous condensation (Scheme 82) of the inherently unstable[141] 5-amino-1H-imidazole (329) with 1,1,3,3-tetramethoxypropane (330) provides access to the parent imidazo[1,5-a]pyrimidine (331).[142] Using an identical approach Novinson et al [143] have also studied the synthesis and reactivity of a variety of imidazo[1,5-a]pyrimidine derivatives. The herbicidal activity of a perchloro derivative (333) of the imidazo[1,5-a]pyrimidine ring system formed by exhaustive chlorination (Scheme 83) of the imidazole derivative (332) has been described in a patent.[144] Derivatives of the imidazo-



(332) (333)

Scheme 83

[1,5-a]pyrimidine ring system have also been the subject of patents[145,146] claiming anxiolytic (tranquilizing) properties. All of the imidazo[1,5-a]pyrimidine syntheses reported to date (see before) employ the common synthetic strategy of starting with a functionalised 4-aminoimidazole derivative and building on the fused pyrimidine ring by suitable condensation reactions. However this approach suffers from the serious drawback that the 4-aminoimidazoles required as starting materials are not

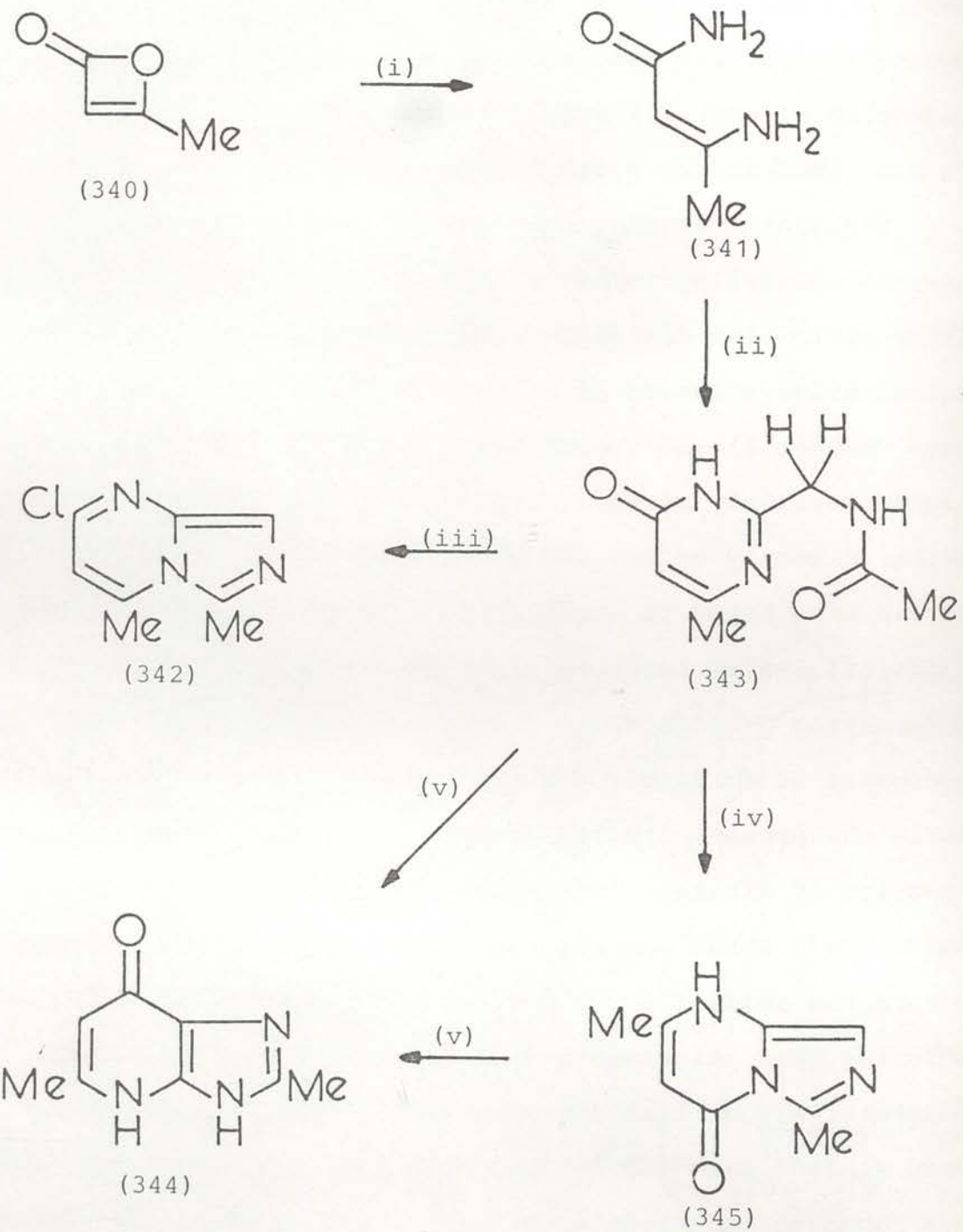


(i) HCl
(ii) NH_3
(iii) NaN_3
(iv) [H]

Scheme 84

readily accessible and are relatively unstable. To make imidazo[1,5-a]pyrimidine derivatives more generally and readily available for biological evaluation as scrambled purines a new synthetic approach was required. The development and implementation of such a flexible imidazo[1,5-a]pyrimidine synthesis is described in the present chapter.

The synthetic strategy adopted (Scheme 84) employed 2-(α-chlorobenzyl)pyrimidines (335) as key starting materials. These pyrimidine derivatives were readily available by the chlorinative scission of 1,2,3-triazolo[1,5-a]pyrimidines (334) (see Chapter 2) and though their chemistry had not been investigated previously it was expected that they could be converted either directly or via the azides (337) into the amines (336). It was then hoped to elaborate the latter to give the respective imidazo[1,5-a]pyrimidines (338) and in particular the biologically interesting C-nucleosides (339). A similar, but less flexible synthesis of imidazo[1,5-a]pyrimidines (Scheme 85) was described[147] while the present studies were in progress. This involved the reaction of diketene (340) with ammonia to give 3-aminocrotonamide (341) which was reacted with ethyl N-acetylglycinate to afford the amide (343) and thence, by cyclisation with phosphoryl chloride, the chlorinated imidazo[1,5-a]pyrimidine (342). Alternatively cyclisation of the amide (343) in polyphosphoric acid at 110° gave the imidazo[1,5-a]pyrimidinone (345) which was found to isomerise in polyphosphoric acid at 180-190° to give the imidazo[4,5-b]pyrimidine derivative (344). This rearrangement can be explained by an acyl migration from N-5 to C-8 in the imidazo[1,5-a]pyrimidine (345).



(i) NH_3

(ii) $EtO_2CCH_2NHCOMe$

(iii) $POCl_3$

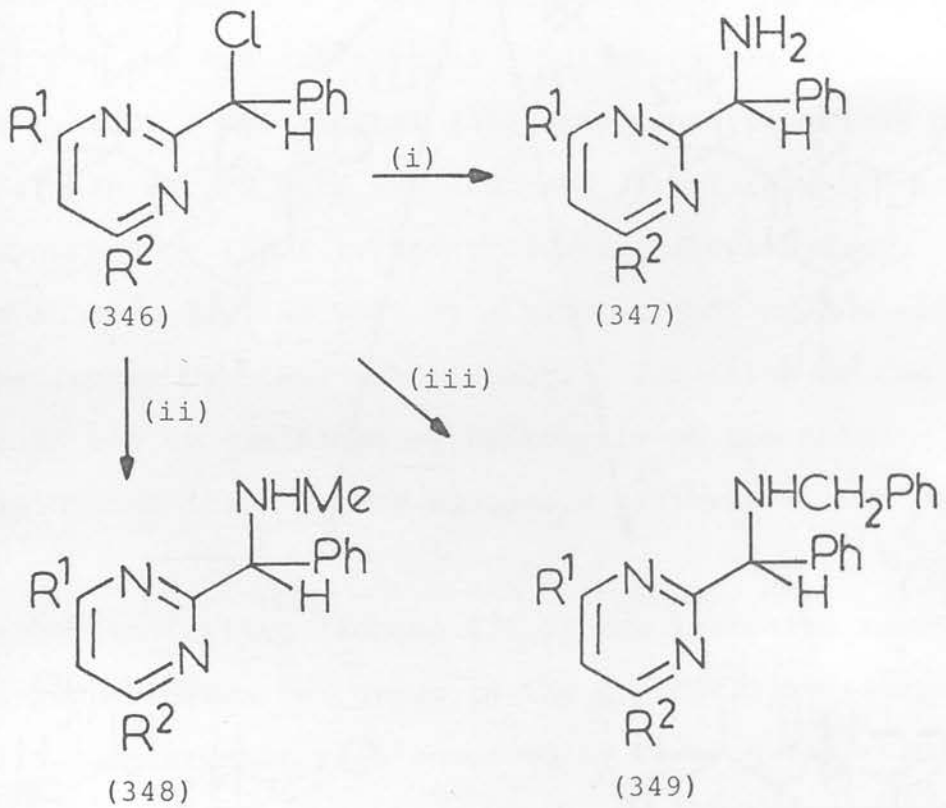
(iv) polyphosphoric acid/110°

(v) polyphosphoric acid/180-190°

Scheme 85

3.2 A Study of the Reactions of 2-(α-Chlorobenzyl)pyrimidines with Nitrogen Nucleophiles

As already indicated, 2-(α-chlorobenzyl)pyrimidines are generally available by the triazole scission of 1,2,3-triazolo-[1,5-a]pyrimidines in acid and being analogues of benzhydryl chlorides should react with a wide range of nitrogen nucleophiles to give the corresponding substitution products. Thus (Scheme 86) it was expected that reaction of the chlorobenzylpyrimidine



(i) NH_3

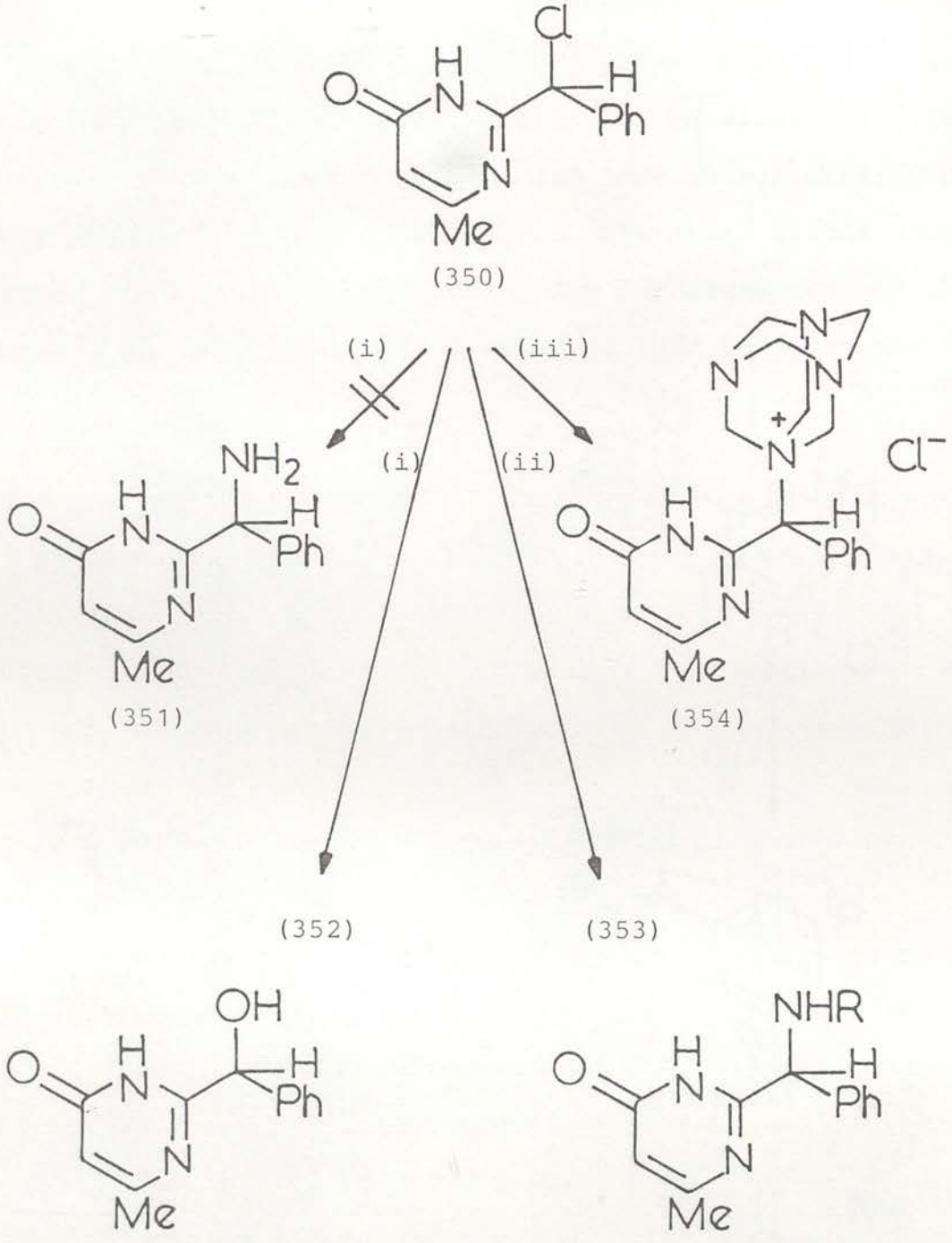
(ii) $MeNH_2$

(iii) $PhCH_2NH_2$

	R^1	R^2
a;	Me	Me
b;	Me	H
c;	H	H

Scheme 86

(346a) (see Chapter 2) with ammonia and primary amines would provide ready access to the amines (347a-349a) valuable as



(i) NH_3

(ii) RNH_2

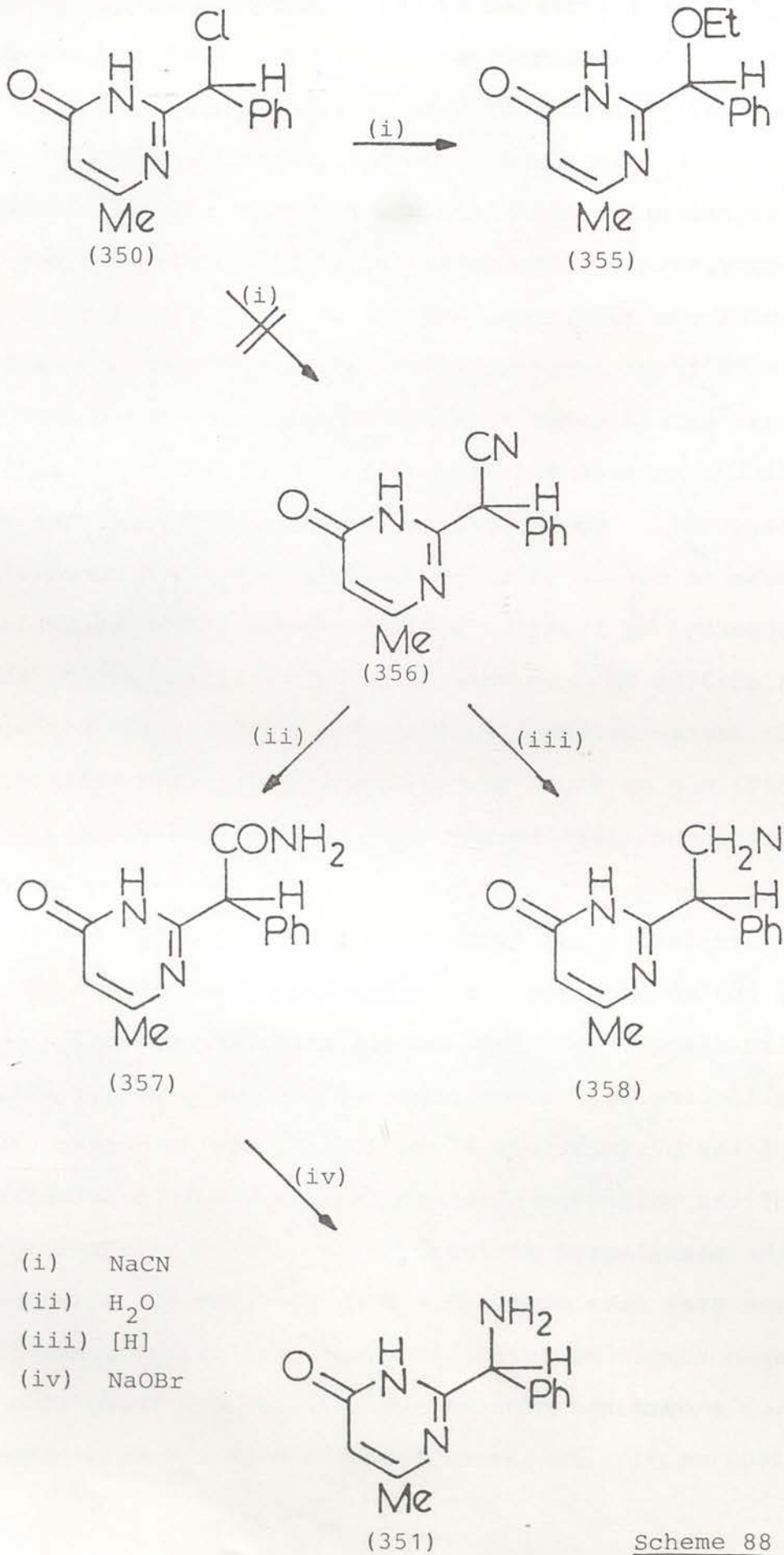
(iii) $(CH_2)_6N_4$

	R
a;	Me
b;	CH_2Ph

Scheme 87

synthetic precursors of imidazo[1,5-a]pyrimidine derivatives. In practice the chloro-compound (346a) was recovered unchanged in high yield after treatment with gaseous ammonia under pressure. The chloro-compound (346a) also failed to give the aminobenzylpyrimidines (348a and 349a) by reaction with methylamine or benzylamine. In contrast (Scheme 87) the chlorobenzylpyrimidinone (350) available by chlorinative scission of the respective triazolopyrimidinone (see Chapter 2) did react with gaseous ammonia under pressure but gave not the hoped-for amine (351) but instead the alcohol (352) which was isolated in moderate yield. The alcohol (352) gave analytical and mass spectral data in accord with the assigned structure which is further supported by its i.r. spectrum which shows hydroxy absorption at 3250 cm^{-1} as well as a band at 1650 cm^{-1} attributable to the lactam carbonyl substituent. Formation of the alcohol (352) can be explained by hydrolysis of the chlorobenzylpyrimidinone (350) in the aqueous alkaline medium during work-up.

A further indication (Scheme 87) of the increased susceptibility of the chlorobenzyl group in the pyrimidinone (350) to nucleophilic displacement when compared to that in the chlorobenzylpyrimidine [Scheme 86; (346a)] was demonstrated by the ready reaction of the pyrimidinone (350) with primary amines. Thus reaction of the chlorobenzylpyrimidinone (350) with methylamine afforded the methylamino product (353a) which gave analytical and mass spectral data consistent with the assigned structure. This was also supported by the i.r. spectrum of the product (353a) which showed the expected NH and carbonyl absorption at 3200 and 2600 cm^{-1}. Further confirmation of the methylamine



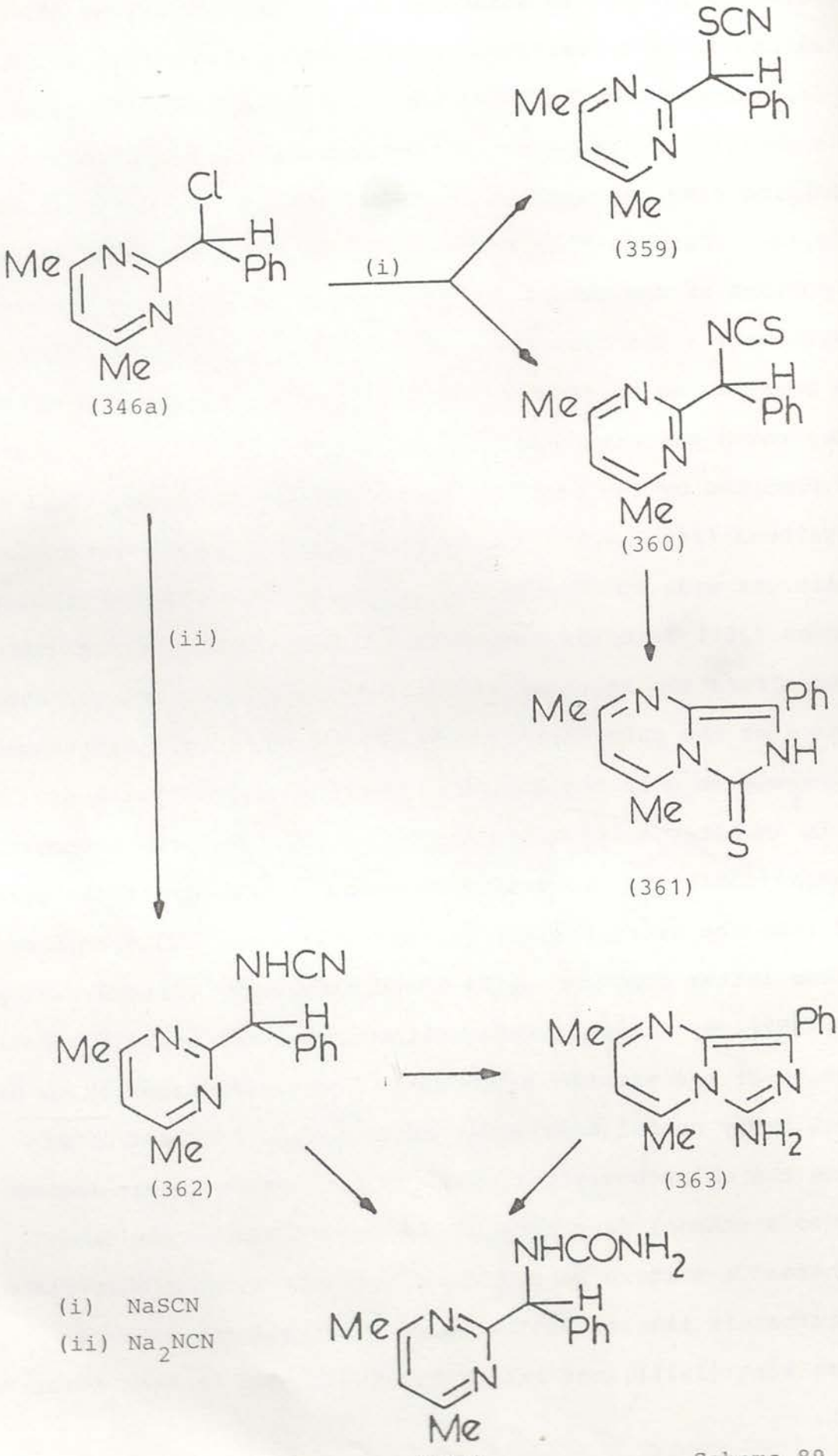
(i) NaCN
(ii) H_2O
(iii) [H]
(iv) NaOBr

Scheme 88

structure (353a) was provided by the ^{1}H n.m.r. spectrum of the compound which exhibited two three-proton singlets at δ2.10 and δ2.30 attributable to the N-methyl and C-6 methyl groups and a one-proton singlet at δ6.00, assigned to H-5 of the pyrimidine ring, as well as a relatively shielded benzylic proton at δ4.45. Surprisingly there was no apparent coupling between the protons of the methyl and NH components of the methylamino substituent. The chlorobenzylpyrimidinone (350) also reacted with benzylamine to give a low yield of the benzylamino-compound (353b) which was characterised as the picrate.

Prompted by the failure of the chlorobenzylpyrimidine derivatives (346a) and (350) to react directly with ammonia an attempt was made to convert the seemingly more reactive chloro-compound (350) into the hexamine salt (354) hydrolysis of which should afford the required amine (351). However the attempted reaction of the chlorobenzylpyrimidinone (350) with hexamethylene-tetramine gave only the starting material in good yield.

In an alternative approach (Scheme 88) to the synthesis of the amine (351) the conversion of the chlorobenzylpyrimidinone (350) into the nitrile (356) was investigated. It was hoped that the latter compound could be converted through the derived amide (357), by Hofmann rearrangement, into the amine (351). Reduction of the nitrile (356) would also provide access to the synthetically useful homologous amine (358). In practice heating the chlorobenzylpyrimidinone (350) with sodium cyanide in aqueous ethanol gave none of the hoped-for nitrile (356) but instead a mixture of two products identified by comparison with authentic samples as the ether (355) and the alcohol [Scheme 87; (352)], the latter being obtained in only minor amount.



(i) NaSCN

(ii) Na_2NCN

Scheme 89

The unexpected resistance of the chlorobenzylpyrimidines (346a) and (350) to amination may be as a consequence of steric hindrance of the incoming amine by both the phenyl and pyrimidine groups attached to the benzylic C-atom. To test this hypothesis it was decided to attempt the displacement of the chlorine substituent in the chlorobenzylpyrimidines (346a) and (350) with linear pseudohalogen-type nucleophilic reagents (NaSCN; Na_2NCN; NaN_3).

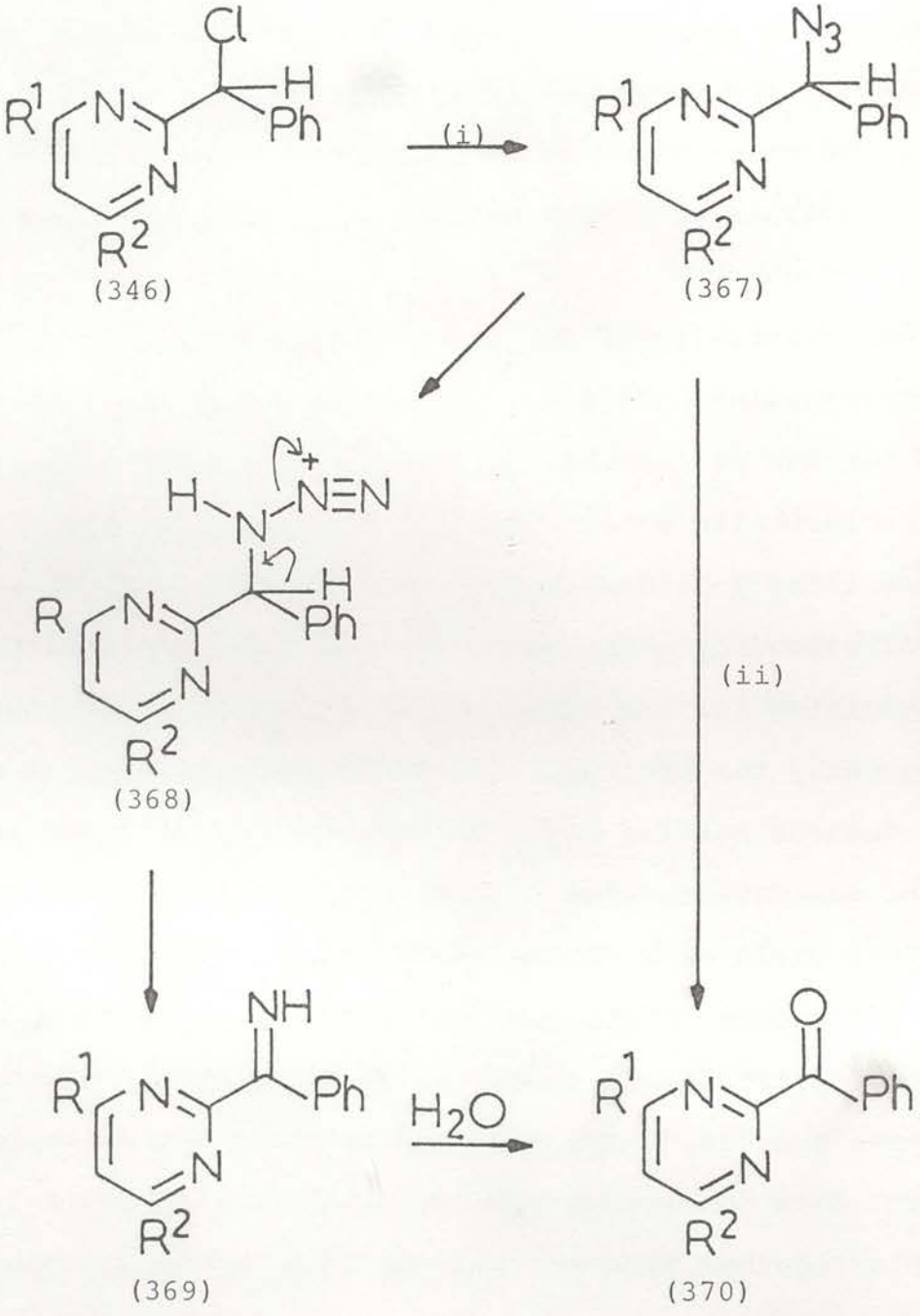
Thus the chloro-compound (346a) was heated with sodium thiocyanate in aqueous ethanol to afford, after chromatography, a product whose elemental analysis and mass spectrum agreed on the molecular formula $C_{14}H_{13}N_3S$ (m/e 255). The ^1H n.m.r. spectrum of the product exhibited a six-proton singlet at δ2.44 and a one-proton aromatic singlet at δ6.92 indicative of the presence of a 2-substituted-4,6-dimethylpyrimidine ring. The n.m.r. spectrum also showed proton resonances due to a phenyl group and a one-proton singlet at δ5.76 ascribed to a benzylic proton. The substance must therefore be either the thiocyanate (359) or the isothiocyanate (360) and on the basis of the i.r. spectrum, which shows a triple-bond absorption at 2160 cm^{-1}, the compound is tentatively assigned the former structure. Furthermore the alternative isothiocyanate compound (360) would be expected to cyclise spontaneously to the imidazopyrimidine-thione (361) none of which was observed in this case. This contrasts with the preparation of the imidazopyrimidinethione (361) by treatment of the BF_3-triazolopyrimidine complex with NaSCN (see Chapter 2) however this might be explained by the BF_3 present in the latter case catalysing a thiocyanate to isothiocyanate rearrangement [(359)→(360)] and hence cyclisation

to the bicyclic thione (361).

When the chlorobenzylpyrimidine (346a) was reacted with disodium cyanamide in aqueous ethanol a complex gum was obtained from which only a trace amount of a product was isolated. The compound showed a parent ion in its mass spectrum at m/e 256 which might be attributed to the urea (364) derived from hydrolysis of either of the expected products (362) or (363) (Scheme 89).

The reactivity of the chlorine substituent in the chlorobenzylpyrimidines (346a-c) and (350) towards displacement by azide ion was of interest not only as a further example of such nucleophilic substitution but also because reduction of the resulting α-azidobenzylpyrimidines might provide access to the corresponding α-aminobenzylpyrimidines required as key intermediates for the synthesis of imidazo[1,5-a]pyrimidines. Consequently the behaviour of the chlorobenzylpyrimidinone (350) towards heating under reflux with sodium azide in aqueous ethanol was investigated. This reaction (Scheme 90) gave an excellent yield of a yellow product which did not however show azide absorption in its i.r. spectrum but instead a band at 1675 cm^{-1} attributable solely to the presence of the pyrimidin-4(3H)-one nucleus. The compound gave analytical and mass spectral data consistent with the molecular formula $C_{12}H_{10}N_2O_2$ and this together with the lack of benzylic proton resonances in its ^1H n.m.r. spectrum allowed the assignment of the ketone structure (366). The presence of only a single carbonyl band in the i.r. spectrum of the ketone (366) must be due to the coincidence of the pyrimidinone and ketonic carbonyl absorptions.

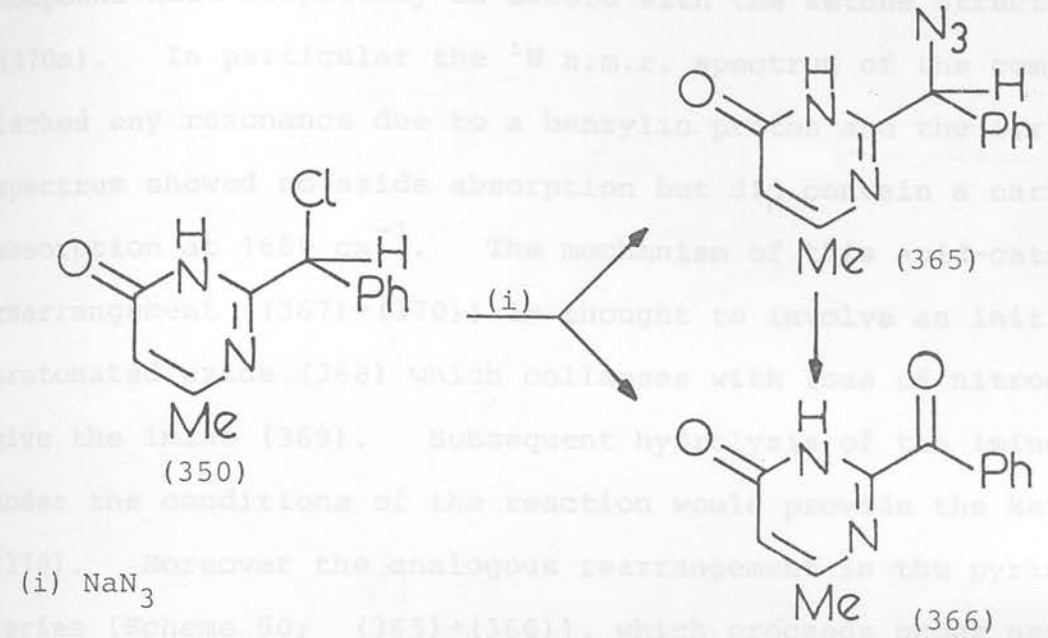
The formation of the ketone (366) from the chlorobenzyl-



(i) NaN_3
(ii) dil.HCl

	R^1	R^2
a;	Me	Me
b;	Me	H
c;	H	H

Scheme 91



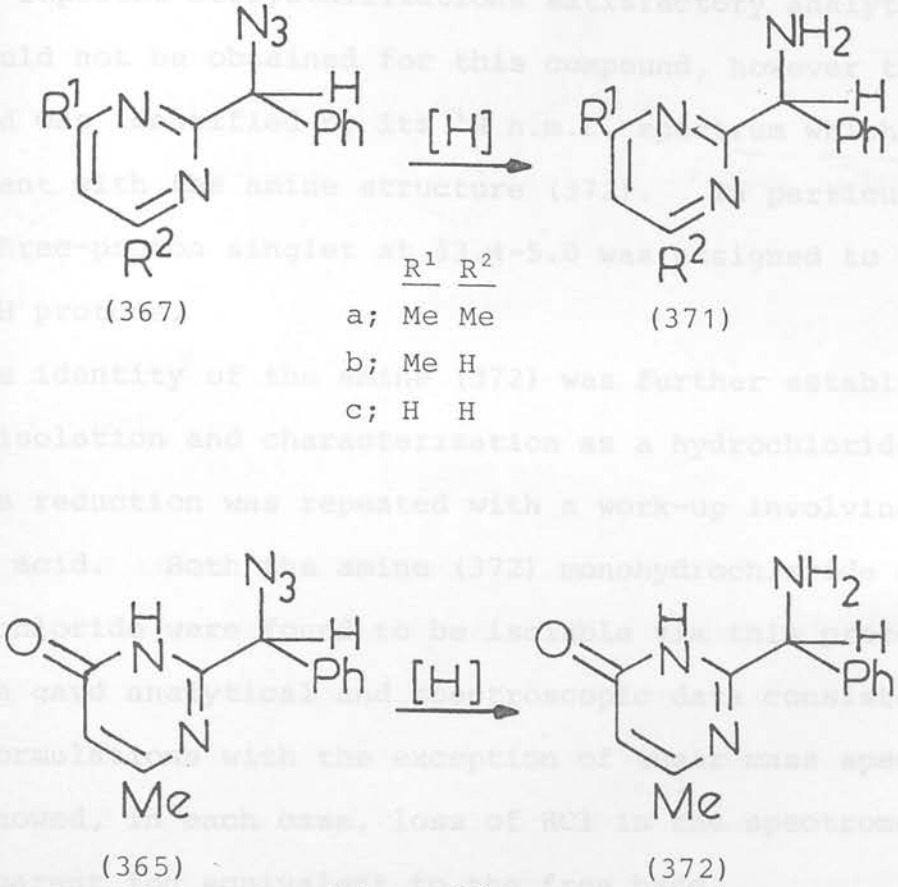
Scheme 90

pyrimidinone (350) by treatment with sodium azide can be explained by initial formation of the azide (365) followed by either a thermal or an acid-catalysed rearrangement and hydrolysis. Indeed when the reaction was repeated at room temperature the intermediate azido-compound (365) was isolated in good yield suggesting that the azide to ketone rearrangement had been thermally promoted. Conversely when the chloro-compounds (346a-c) were heated with sodium azide in aqueous ethanol (Scheme 91) the azides (367a-c) were isolated in excellent yields. Analytical and spectroscopic data for all three azides (367a-c) were fully in accord with their structures and thus it appeared that the azides were thermally stable. Furthermore when the azide (367a) was heated with ethanolic hydrochloric acid (or glacial acetic acid) a cream solid was isolated in good yield. Elemental analysis provided the molecular formula $C_{13}H_{12}N_2O$ in agreement with the mass spectrum parent ion at m/e 212 and the spectroscopic properties of the

compound were completely in accord with the ketone structure (370a). In particular the ^1H n.m.r. spectrum of the compound lacked any resonance due to a benzylic proton and the i.r. spectrum showed no azide absorption but did contain a carbonyl absorption at 1680 cm^{-1}. The mechanism of this acid-catalysed rearrangement [(367)→(370)] is thought to involve an initial protonated azide (368) which collapses with loss of nitrogen to give the imine (369). Subsequent hydrolysis of the imine (369) under the conditions of the reaction would provide the ketone (370). Moreover the analogous rearrangement in the pyrimidinone series [Scheme 90; (365)→(366)], which proceeds under neutral conditions, may occur through a similar mechanism in which the reaction is auto-catalysed by the relatively acidic pyrimidinone NH proton.

2-Pyrimidinyl ketones [e.g. (360) and (370)] are extremely rare and it was therefore of interest to investigate their chemical behaviour (see Section 3.3). Also the azido-compounds [e.g. (365) and (367a-c)] are potential precursors to the key intermediate amines [e.g. Scheme 92; (371a-c) and (372)] and therefore attention was directed to the reduction of these compounds.

When the azide (367a) was heated in ethanol with sodium dithionite a good yield of the starting azide was recovered and similarly the azide (367a) failed to react with sulphur dioxide. However when the azide (367a) was subjected to medium pressure (4 atm) hydrogenation over 10% palladium-on-charcoal a product was formed in quantitative yield. The substance showed only NH absorptions in its i.r. spectrum and elemental analysis provided the molecular formula $C_{13}H_{15}N_3$ in agreement with its mass spectrum (m/e 213). Confirmation of the amine structure



(367) (371)

	R^1	R^2
a;	Me	Me
b;	Me	H
c;	H	H

(365) (372)

Scheme 92

(371a) was obtained from the ^{1}H n.m.r. spectrum of the compound which displayed a six-proton singlet at δ2.40 as well as a one-proton singlet at δ6.78 attributable to the dimethylpyrimidine protons. In addition to a phenyl group, the spectrum also contained a one-proton singlet at δ5.20 which was assigned to a comparatively shielded benzylic proton. The analogous amines (371b) and (371c) were also prepared by the identical hydrogenolysis of the azides (367b) and (367c) and their spectroscopic and analytical data was entirely consistent with the assigned structures.

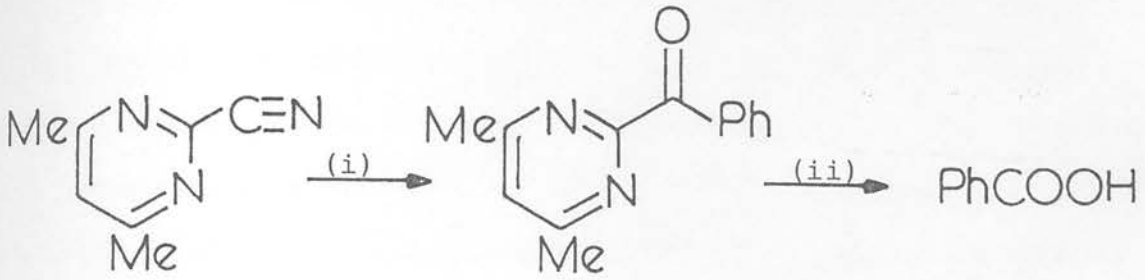
A similar reduction of the azidobenzylpyrimidinone (367) gave a product whose mass spectrum showed a parent ion at m/e 213 and whose i.r. spectrum showed a variety of NH absorptions.

Despite repeated recrystallizations satisfactory analytical data could not be obtained for this compound, however the compound was identified by its ^{1}H n.m.r. spectrum which was consistent with the amine structure (372). In particular a broad three-proton singlet at δ3.4-5.0 was assigned to the three NH protons.

The identity of the amine (372) was further established by its isolation and characterisation as a hydrochloride salt when the reduction was repeated with a work-up involving hydrochloric acid. Both the amine (372) monohydrochloride and dihydrochloride were found to be isolable via this procedure and both gave analytical and spectroscopic data consistent with their formulations with the exception of their mass spectra which showed, in each case, loss of HCl in the spectrometer to give a parent ion equivalent to the free base.

3.3 Some Studies on the Reactivity of 2-Pyrimidinyl Ketones

Reports on the synthesis and reactivity of 2-pyrimidinyl ketones in the literature are extremely rare[148,149] and it was therefore of interest to investigate the reactivity of the examples of this type of compound prepared previously (see Section 3.2). Klotzer[148] has reacted the nitrile (373) with phenyl magnesium bromide (Scheme 93) to obtain the ketone (370a). Moreover when the ketone (370a) was oxidised with potassium permanganate only benzoic acid could be isolated and a similar result was obtained during the course of these studies. Thus when the ketone (366) was treated with hydrogen peroxide at 50° (Scheme 94) only benzoic acid was isolated. This result is



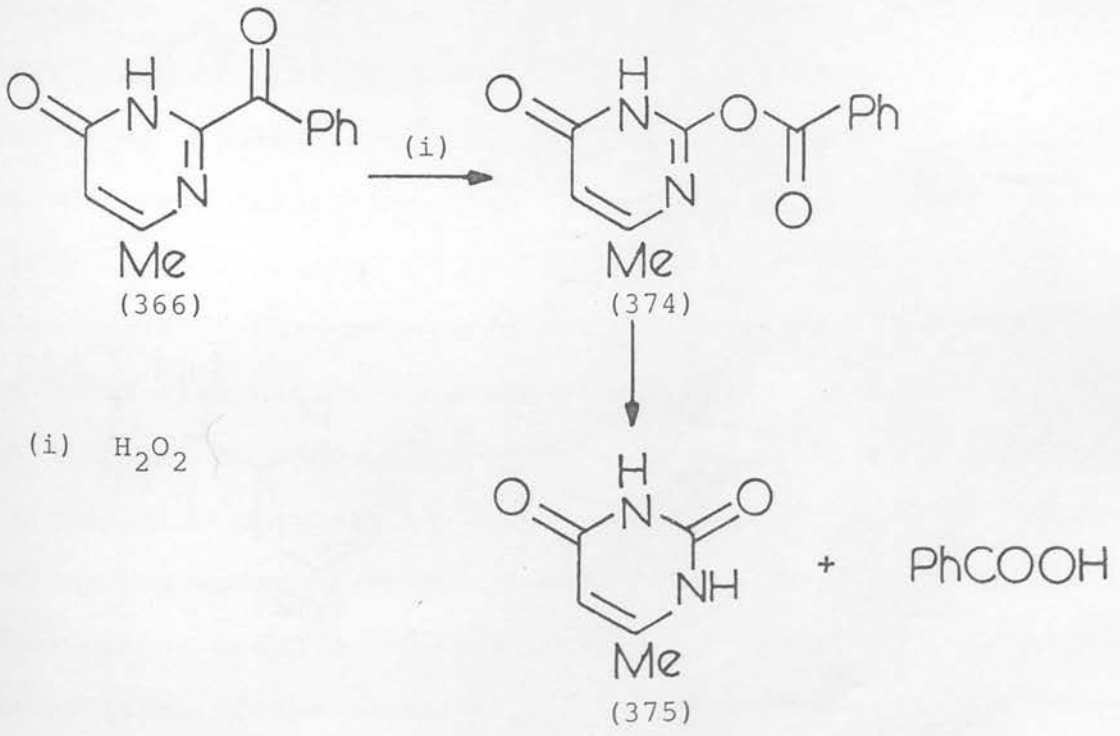
(373) (370a)

(i) PhMgBr

(ii) $KMnO_4$

Scheme 93

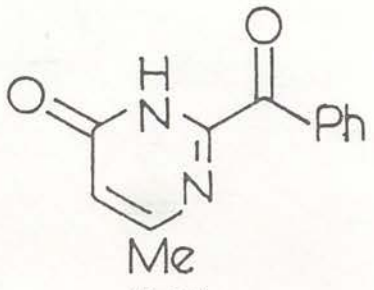
explicable in terms of a Baeyer-Villiger oxidation of the ketone (366) to produce the ester (374), subsequent hydrolysis of which would afford benzoic acid. Although the other expected product, 6-methyluracil (375), was not isolated the good yield of benzoic acid obtained does suggest that the pyrimidinone ring migrates preferentially to the electron-deficient oxygen atom.



(366) (374) (375)

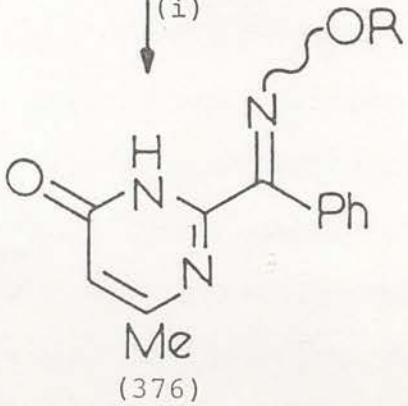
(i) H_2O_2

Scheme 94



(366)

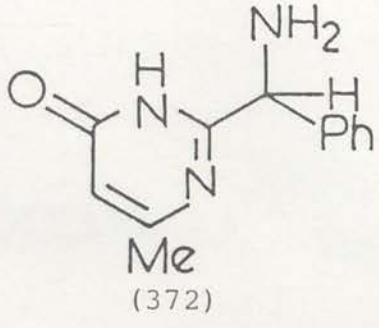
(i)



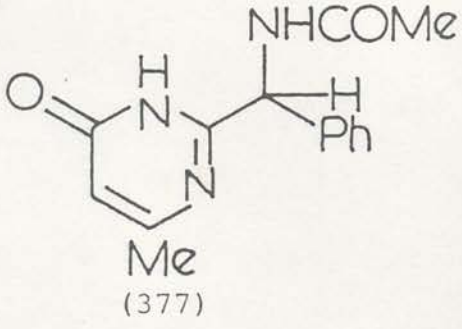
(376)

R	
a;	H
b;	COMe
c;	COPh
d;	SO_2T
e;	CO_2Et

(ii)



(372)



(377)

(i) NH_2OH

(ii) [H]

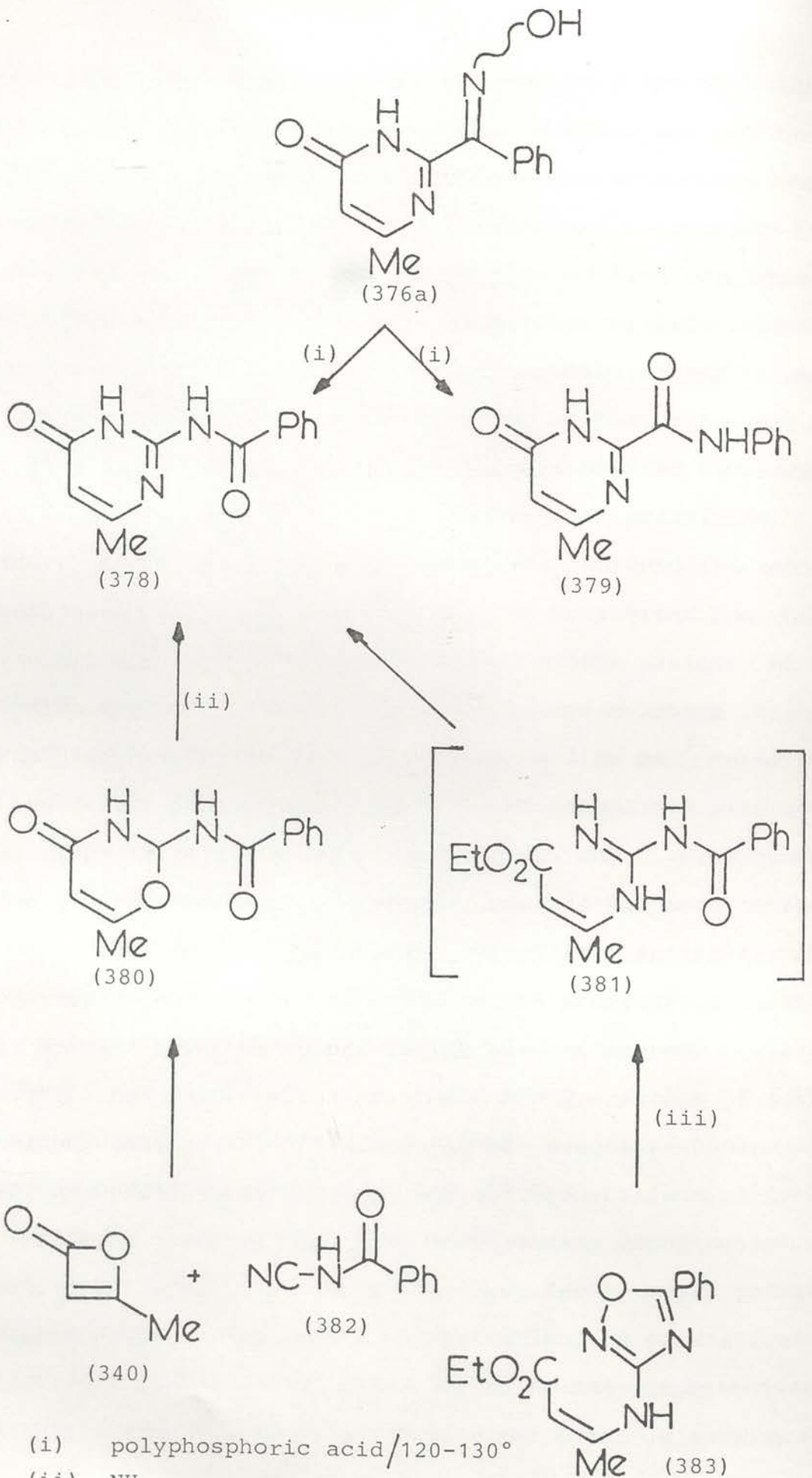
Scheme 95

To investigate the reactivity of 2-pyrimidinyl ketones it was decided to prepare some ketone derivatives in particular hydrazones and oximes. The ketone (366) was therefore reacted with hydroxylamine (Scheme 95) to give a solid product in excellent yield. The i.r. spectrum of the compound displayed both NH and carbonyl absorptions and analytical data provided the molecular formula $C_{12}H_{11}N_3O_2$ (m/e 229). Although the ^1H n.m.r. spectrum of the compound confirmed the oxime structure (376a) the spectrum also suggested the presence of two isomers. Thus while the phenyl group appeared as a singlet at δ7.39 and the oxime OH as a broad singlet at δ9.00-9.60 both the C-6 methyl and H-5 were recorded as doublets. Additionally, on expansion, the H-5 doublet was shown to consist of two quartets and as irradiation at the C-6 methyl resonance removed this multiplicity the observation can be attributed to coupling between the C-6 methyl protons and H-5. However increasing the temperature at which the ^1H n.m.r. spectrum was recorded to 103° did not cause coalescence of the doublets (either that derived from the C-6 methyl group or that of H-5) and this is explicable by the presence of stable E and Z isomers. As exact analytical figures could not be obtained for this isomeric mixture it was decided to prove the structure of the oxime (376a) by further chemical manipulation. Moreover reduction of the oxime (376a) would provide an alternative synthetic route to the amine (372).

Attempts to reduce the oxime (376a) by catalytic hydrogenation at atmospheric pressure or at 4 or 6 atm returned only starting material and sodium dithionite also failed to reduce the oxime (376a) either under neutral or alkaline conditions. Catalytic hydrogenation of the oxime (376a) in the presence of glacial

acetic acid was also unsuccessful although in this case only one of the two isomeric oximes, whose analytical and spectroscopic properties are entirely consistent with a single isomer, was recovered. Repetition of the reaction using concentrated hydrochloric acid to trap the desired product also returned unchanged starting material. The observed resistance of the oxime (376a) to reduction was surprising and therefore attention was instead turned to the preparation of a series of oxime derivatives bearing substituents on the oxime oxygen atom.

Acetylation of the oxime (376a) with acetic anhydride (Scheme 95) provided the oxime acetate (376b), albeit in poor yield, and analytical and spectroscopic data for this compound are in complete accord with its assigned structure. In particular its i.r. spectrum exhibited a high frequency carbonyl absorption at 1780 cm^{-1} as well as another at 1685 cm^{-1} and these absorptions were attributed to the O-acetyl moiety and the ring amide respectively. The low yield of product (376b) obtained in this reaction prompted attempts to prepare the oxime-acetate (376b) under different conditions. However acetic anhydride acetylation under acid catalysis failed completely to give the oxime-acetate (376b). Conversely base catalysis did give the desired product (376b) in moderate yield but in this case the product could not be obtained in a pure state. Prolonged heating of the oxime (376a) in acetic anhydride was shown to cause decomposition to a multicomponent mixture from which only a small amount of the starting oxime (376a) could be recovered. Furthermore while an approach to the oxime acetate (376b) by the triethylamine catalysed condensation of the oxime (376a) with acetyl chloride was successful again the product (376b) was obtained only in low



(i) polyphosphoric acid/120-130°

(ii) NH_3

(iii) H_2, Pd/C

Scheme 96

yield. On the basis that the acetoxy group is a better leaving group than the hydroxy group it was thought that the oxime-acetate (376b) might be more easily reduced to the amine (372) than the parent. In practice hydrogenation of the oxime-acetate (376b) provided a mixture of the desired amine (372) and the acetamide (377). The acetamide (377) is thought to be a condensation product of the expected amine (372) and acetic acid produced as a by-product of the reduction and this amide (377) has also been prepared by the direct action of acetic acid on the amine (372) (see later).

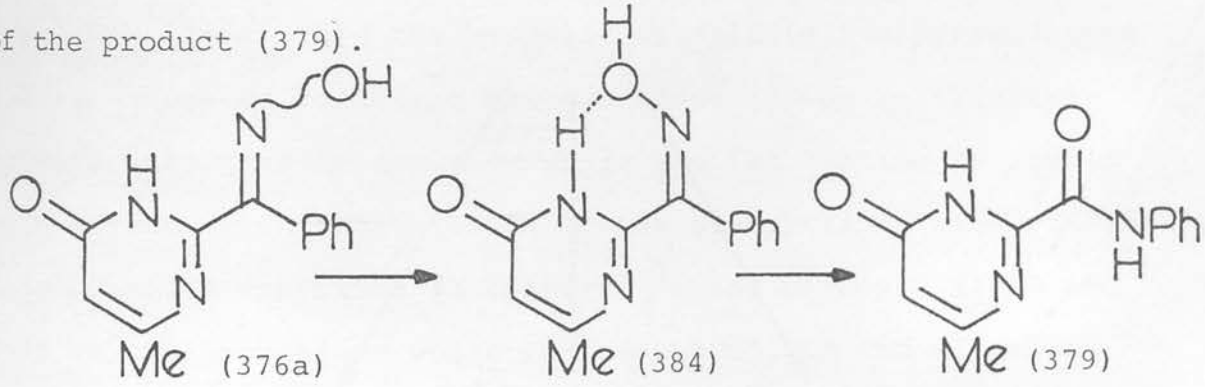
Further examples of O-substitution of the oxime (376b) were obtained (Scheme 95) by the triethylamine catalysed condensation of the oxime (376a) with benzoyl chloride, p-toluenesulphonyl (tosyl) chloride and ethyl chloroformate. Thus the oxime benzoate (376c) and the oxime-tosylate (376d) were both obtained in fair yield while the ethyl oxime-carboxylate (376e) was isolated in rather lower yield and all three oxime derivatives showed analytical and spectroscopic properties entirely consistent with their assigned structures.

A typical reaction of oximes is the Beckmann rearrangement and such reaction (Scheme 96) of the oxime (376a), which is an isomeric mixture, should give both amides (378) and (379). However when the oxime (376a) was heated in polyphosphoric acid at 120-130° for 10 min a single product was isolated in 70% yield. The compound analysed for the molecular formula $C_{12}H_{11}N_3O_2$ and exhibited a parent ion at m/e 229 in its mass spectrum. The i.r. spectrum of the product contained both carbonyl absorptions as a broad peak between 1650 and 1700 cm^{-1} and did not help to distinguish between the two possible products

(378) and (379). Resonances at δ2.36 and δ6.42 in the ^{1}H n.m.r. spectrum of the compound were attributed to the C-6 methyl group and H-5 of the pyrimidine ring while, in addition to a phenyl group at δ7.10-7.80, the spectrum also showed two NH resonances at δ9.50 and δ7.00-8.20. Of the two isomers which are possible products only the N-benzoyl isomer (378) has been reported previously (i.e. the product which would arise from a preferential migration of the pyrimidine ring to the electron deficient nitrogen atom). Thus Girault et al [150] have demonstrated (Scheme 96) that the oxazinone (380), prepared from diketene (340) and N-benzoylcyanamide (382), reacted with ammonia to provide the 2-benzamidopyrimidinone (378). A completely different route (Scheme 96) to this compound has also been reported by Cusmano et al.[151] On catalytic hydrogenation the N-substituted amino-oxadiazole (383) was shown to convert to the benzamide (378) and this reaction presumably proceeds via the ring-opened intermediate (381). The reported m.p. of 196°C[150] or 198°C[151] for the amide (378) compare with the observed m.p. of 189-192°C for the isolated product however the published ^{1}H n.m.r. details of the amide (378) are in contradiction to those found in this work for the product of Beckmann rearrangement of the oxime (376a). In particular the N-benzoyl compound (378) is reported to exhibit in its ^{1}H n.m.r. spectrum a C-6 methyl resonance at δ2.17 and an H-5 resonance at δ6.00[150] (c.f. δ2.24 and δ5.98[151]). The disagreement of n.m.r. data between the isolated product and the reported N-benzoyl isomer (378) invites the conclusion that the isolated compound is, in fact, the previously unknown N-phenyl isomer (379) obtained by an exclusive phenyl migration. On these

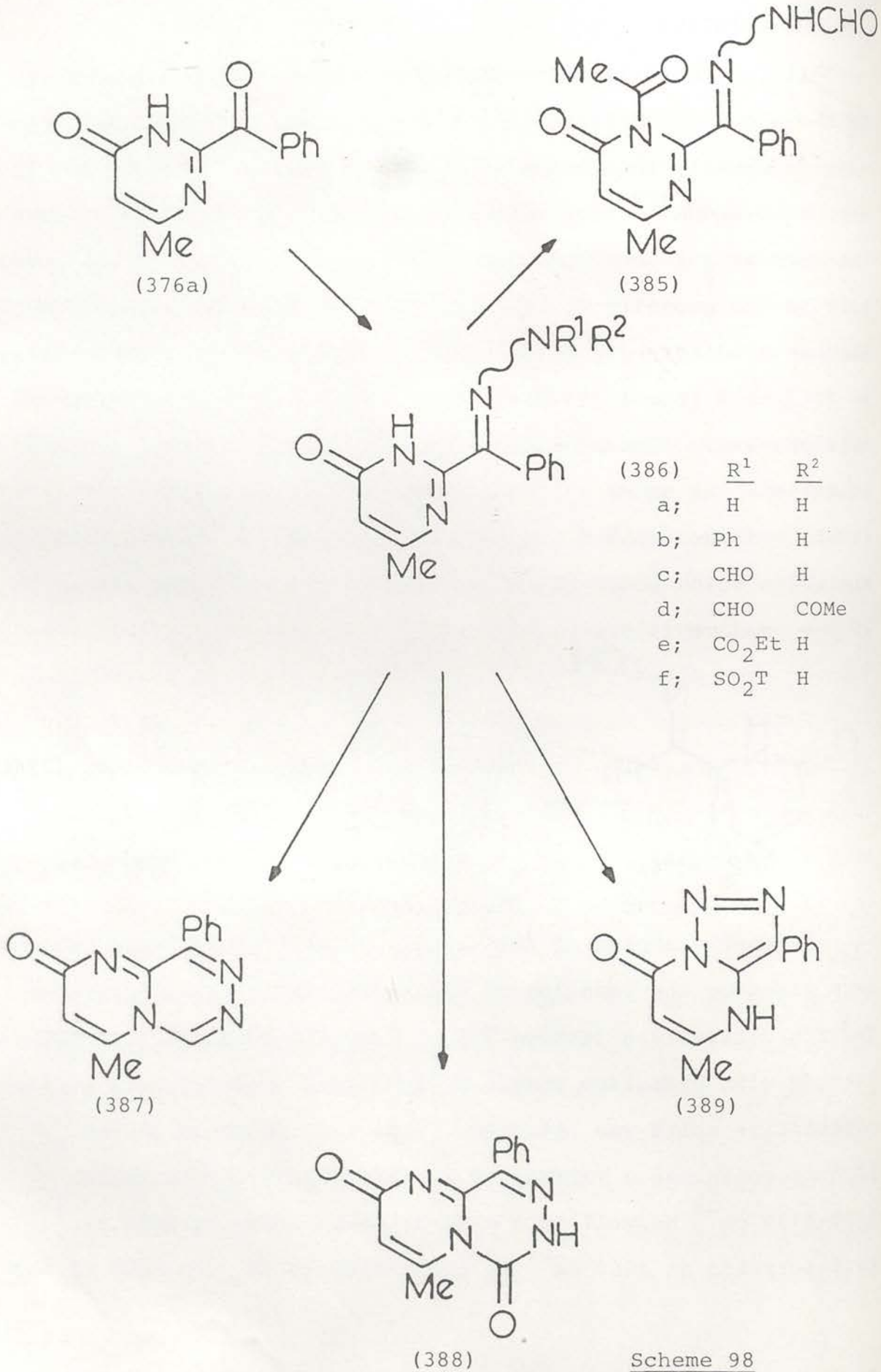
grounds the product is therefore tentatively assigned the structure (379).

It is generally accepted that the group which migrates to the electron deficient nitrogen atom in a Beckmann rearrangement is usually that which is trans to the leaving group but it has also been shown[152] that this is not always the case and in fact the reverse has been observed. It is possible that a rearrangement in the geometry of the oxime can occur prior to the migration and the finding that, in this case, a single product was obtained in 70% yield from a 1:1 mixture of isomers is also evidence for this process. Consequently it may be that under the reaction conditions the oxime (376a) preferentially adopts the more stable hydrogen-bonded conformation [Scheme 97; (384)] prior to migration which would therefore lead to the exclusive formation of the product (379).



Scheme 97

Further examples of the reactivity of 2-pyrimidinyl ketones were provided by the reaction of the ketone (376a) with hydrazine and its derivatives (Scheme 98). When the ketone (376a) was reacted with hydrazine itself an excellent yield of a colourless crystalline solid was obtained. The i.r. spectrum of the product contained a variety of NH absorptions in the region 3400-3100 cm^{-1} as well as a carbonyl absorption at 1680 cm^{-1}. An absorption at 1660 cm^{-1} is attributed to the C=N bond of the


NHCHO
Me
O
N
Ph
Me
(376a)
(385)
NR1R2
(386) R1 R2
a; H H
b; Ph H
c; CHO H
d; CHO COMe
e; CO2Et H
f; SO2T H
Ph
N
NH
(387)
(389)
(388)

Scheme 98

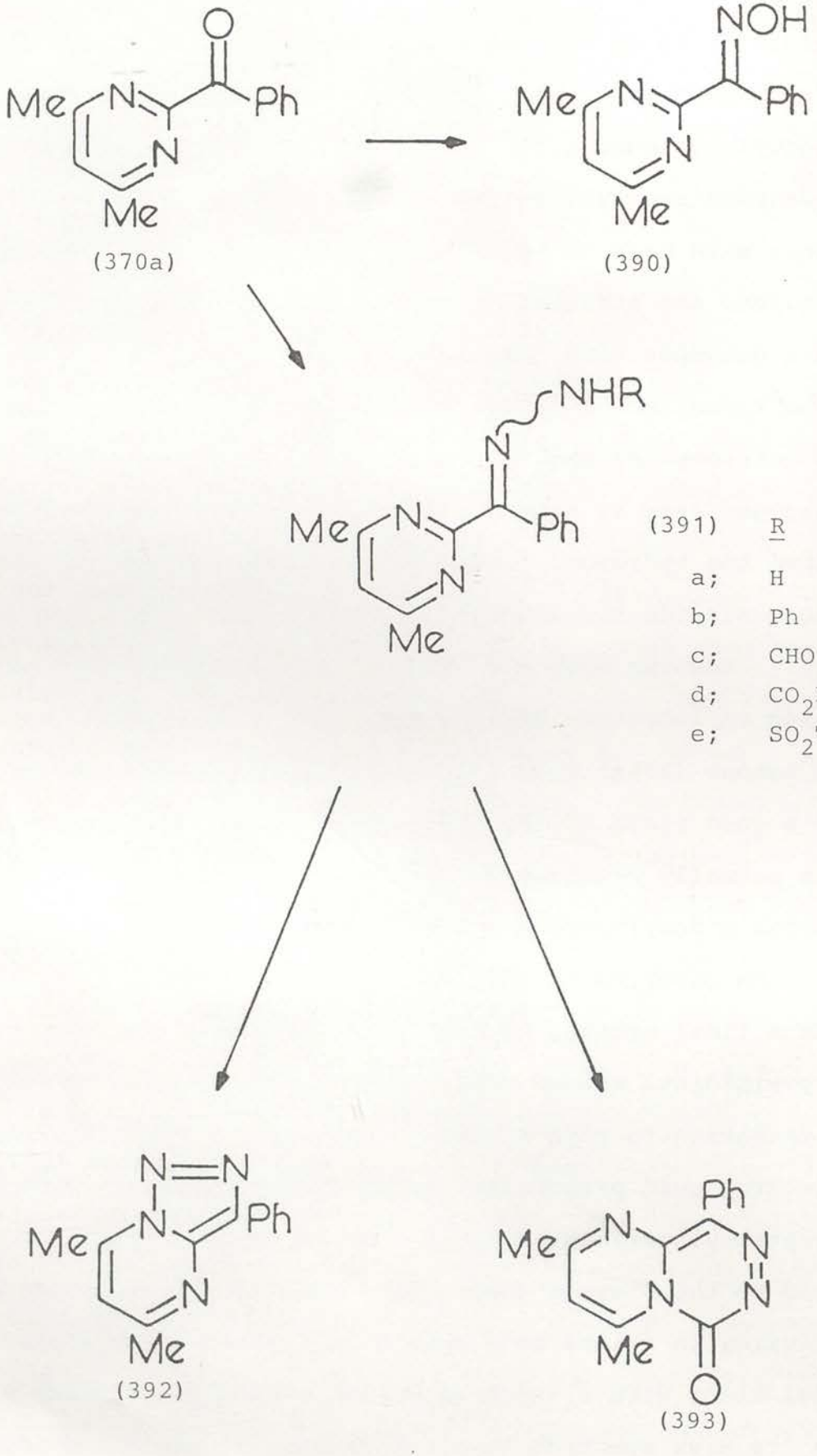
hydrazone group. Elemental analysis of the compound provided the molecular formula $C_{12}H_{12}N_4O$ in line with the anticipated hydrazone structure (386a) and the mass spectrum recorded a parent ion at m/e 228. Confirmation of the structure (386a) was provided by the ^1H n.m.r. spectrum of the compound which contained the C-6 methyl resonance at δ1.98 and the H-5 resonance at δ5.99 as well as a seven-proton multiplet at δ7.60-7.10 for the phenyl group plus the hydrazone NH_2 grouping. Phenylhydrazine reacted with the ketone (Scheme 98) in an identical fashion to give the phenylhydrazone (386b) in good yield and this compound has also been fully characterised.

It was thought that the hydrazone (386a) or its derivatives might be amenable to ring closure to form novel 6-6 bicyclic systems and therefore attempts were made to convert the hydrazone (386a) into the bicyclic triazino[4,5-a]pyrimidinone (387). However refluxing the hydrazone (386a) in triethylorthoformate gave no reaction while similar heating in formic acid gave a quantitative yield of the non-cyclised product (386c). This compound exhibited NH (3120 cm^{-1}) and carbonyl (1720 and 1660 cm^{-1}) absorptions while the mass spectrum and elemental analysis agreed with the molecular formula $C_{13}H_{12}N_4O_2$ (m/e 256). The ^1H n.m.r. spectrum of the compound while suggesting the presence of E and Z isomers, also confirmed the structure as the formylhydrazide (386c). The possibility of dehydrating the initially-formed formylhydrazide (386c) by prolonged heating in formic acid to form the bicycle (387) was explored but it was found that decomposition occurred rather than cyclisation. Moreover treatment of the formylhydrazide (386c) with acetic anhydride caused acetylation rather than dehydration and the

product was shown to be a monoacetyl derivative of the formylhydrazide (386c) by its analytical data ($C_{15}H_{14}N_4O_3$ and m/e 298). However it was not possible to distinguish between the ring-acetyl compound (385) or its isomer (386d). Attempts to cause dehydrative cyclisation of the formylhydrazide (386c) by treatment with base or by reaction with phosphoryl chloride also failed, the starting material being recovered in the former case and decomposition occurring in the latter.

The formation of bridgehead-fused 1,2,3-triazole compounds from N-heterocycles bearing an exocyclic hydrazone group α to the nitrogen atom is a well documented process (see Chapter 1). Thus when the hydrazone (386a) was oxidised (Scheme 98) with manganese dioxide the triazolopyrimidine (389) was the expected product. However when the reaction was attempted in dimethylformamide an inorganic mixture resulted. Conversely treatment of the ketone (376a) with toluene-p-sulphonyl hydrazine did afford a good yield of the triazolopyrimidine (389) and although base is normally required to catalyse the decomposition of the intermediate tosylhydrazone (386f) (see Chapter 1) nevertheless cyclisation occurred in this case in its absence.

In a final attempt to prepare a 6-6 bicyclic system from the 2-pyrimidinyl ketone (376a) the ketone was reacted with ethyl carbazate to give a product (Scheme 98) whose analytical and spectroscopic properties are entirely consistent with the ethoxycarbonylhydrazone (386e). An attempt to convert this compound to the bicycle (388) with thermal elimination of ethanol by refluxing in xylene gave only a good yield of starting material along with a trace amount of a material showing m/e 254 in its mass spectrum (i.e. suggesting it was the product).


Me
N
Ph
N
Me
O
(370a)
NOH
(390)
NHR
(391) R
a; H
b; Ph
c; CHO
d; CO_2Et
e; SO_2T
(392)
(393)

Scheme 99

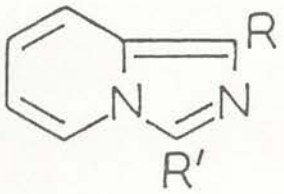
Repetition of the reaction in refluxing dibenzyl ether however gave only a green uncharacterisable solid.

The corresponding 2-pyrimidinyl ketone (370a) has been a known compound since 1956[148] but hitherto the reactivity of this molecule has been little studied. In practice the ketone (370a) displayed reactivity akin to that described above for its analogue (376a). Thus on treatment with hydroxylamine (Scheme 99) the ketone (370a) was converted in excellent yield to the oxime (390) while reaction with hydrazine gave a quantitative yield of the hydrazone (391a) and phenylhydrazine reacted similarly to produce the phenylhydrazone (391b). All three compounds gave analytical and spectroscopic data consistent with their assigned structures with the exception that the hydrazone (391a) did not show a parent ion in its mass spectrum, the highest recorded peak corresponding to M-1. To confirm the structure of the hydrazone (391a) it was decided to prepare the formylated derivative (391c) and on reflux in formic acid the hydrazone (391a) was indeed converted to the formylhydrazone (391c). The i.r. spectrum of the product displayed the expected carbonyl absorption at 1730 cm^{-1} as well as an NH absorption at 3320 cm^{-1}. The mass spectrum recorded the anticipated parent ion at m/e 254 but despite repeated recrystallization correct elemental analysis could not be obtained for this product. However the ^1H n.m.r. spectrum of the formylhydrazone (391c) was consistent with its assigned structure in particular the aldehydic proton appeared as a doublet at δ8.99 coupled to the adjacent NH. On further recrystallization of the formylhydrazone (391c) it was found that hot-filtration removed a trace of an impurity identified by elemental analysis and mass

spectroscopy as N,N'-diformylhydrazide.[143] The structure of the hydrazone (391a) was therefore established by its manganese dioxide oxidation to the triazolopyrimidine (392) in good yield. The triazolopyrimidine (392) could also be formed in good yield by treatment of the ketone (370a) with toluene-p-sulphonyl hydrazone although in this case a trace of the intermediate tosylhydrazide (391e) was also isolated. Analytical and spectroscopic data for the tosylhydrazide (391e) were in accord with its structure with the exception that the highest peak shown in the mass spectrum was m/e 225 (M- SO_2T).

With a view to preparing the bicyclic system (393) the ketone (370a) was heated with ethyl carbazate in a reaction designed to give the ethoxycarbonylhydrazone (391d). However no reaction occurred and the ketone (370a) was recovered in good yield.

Clearly the attempt to employ 2-pyrimidinyl ketones as intermediates for the formation of 6-6 bicyclic systems was meeting with limited success and it was therefore decided to return attention to the initial goal of the preparation of 6-5 bicyclic systems and in particular the anticipation that 2-(α-aminobenzyl)pyrimidine derivatives, which had been synthesised from the corresponding azides (see Section 3.2), could be used to prepare the imidazo[1,5-a]pyrimidine ring system.



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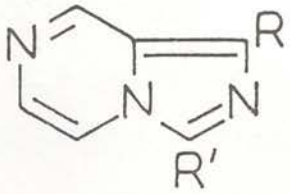

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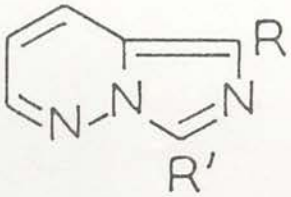

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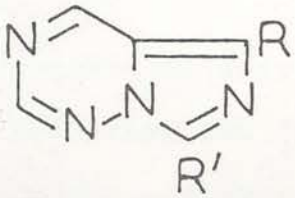

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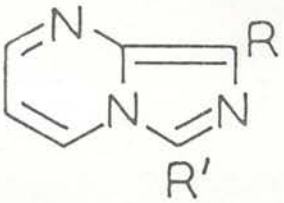
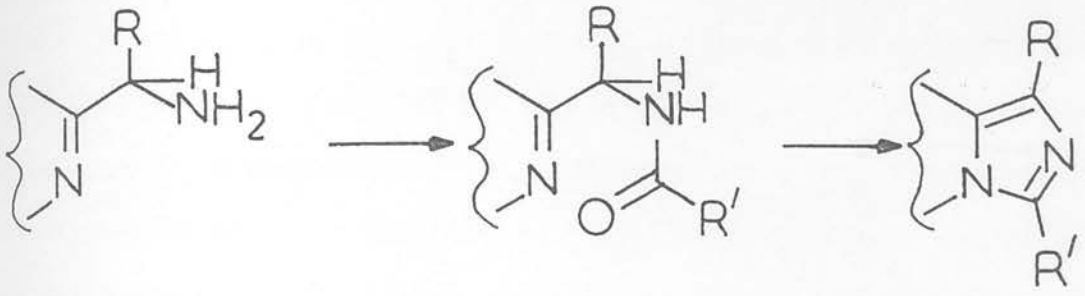


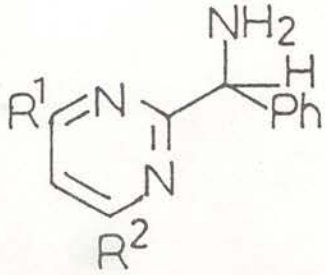
(398)

3.4 Imidazo[1,5-a]pyrimidine



The synthetic strategy of allowing an N-heterocycle, bearing an aminoalkyl group at a position adjacent to a ring nitrogen atom, to be acylated and then subsequently chlorinating the amide unit with rapid cyclisation to afford imidazole-fused products was initially used by Bower and Ramage[125] to prepare imidazo[1,5-a]pyridine derivatives (394). The same methodology was then exploited by Abushanab and his co-workers[132-138] to provide entry to the imidazo[1,5-a]pyrazine ring system (395) and has been further extended to the synthesis of imidazo[1,5-b]pyridazine (396)[154] and imidazo[1,5-f]-1,2,4-triazine (397) derivatives.[155,156] In contrast, prior to the advent of this work, the imidazo[1,5-a]pyrimidine ring system (398) had not been prepared by this synthetic sequence. A pre-requisite to the success of this strategy for the preparation of such imidazopyrimidines is the establishment of a route to 2-aminoalkylpyrimidine compounds and it has been demonstrated that these key intermediates can be obtained in three steps from the corresponding readily available triazolopyrimidines (see Section 3.2).

With the objective of synthesising the imidazopyrimidine nucleus unsubstituted in the 6-position the amine (371a) was heated in neat formic acid to afford a quantitative yield of product. That formylation had occurred was shown by the presence in the i.r. spectrum of an absorption at 1655 cm^{-1}



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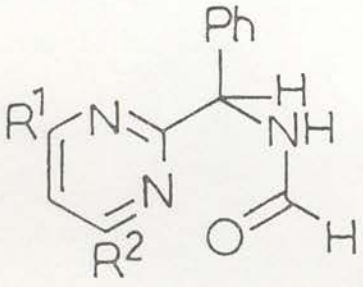

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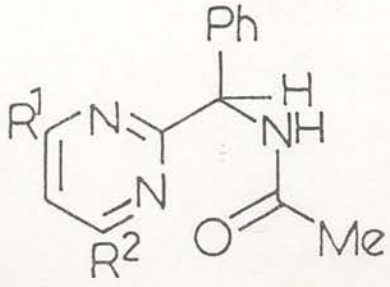
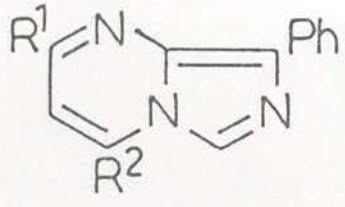


(400)

(401)



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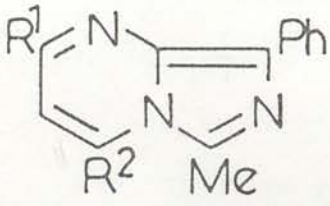

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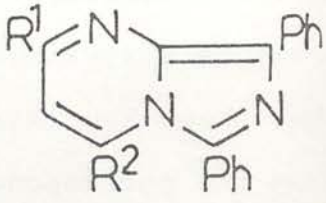


(404)

	R^1	R^2
a;	Me	Me
b;	Me	H
c;	H	H
d;	H	Me

Scheme 100

attributable to an amide carbonyl and analytical data agreed with the formamide structure (399a). Support for the structure (399a) was also obtained by the exhibition in the ^{1}H n.m.r. spectrum of a doublet at δ6.11 coupled to a doublet of doublets δ9.02 which in turn was coupled to another doublet at δ8.16 consistent with the presence of a formamidobenzyl side chain. Subsequent cyclisation was accomplished by treatment of the formamide (399a) with phosphoryl chloride and the bicyclic imidazo[1,5-a]pyrimidine (402a) was obtained in very good yield. In accord with the observed elemental analysis ($C_{14}H_{13}N_3$) the mass spectrum displayed a parent ion at m/e 223 and confirmation of the structure (402a) was obtained by the ^{1}H n.m.r. spectrum of the product and in particular the appearance therein of a one-proton singlet at δ8.35 attributable to H-6. The imidazo-[1,5-a]pyrimidine nucleus is nominally a 10 π electron aromatic ring system however the existence of a degree of bond fixation in the system is evidenced by the observation that the resonance at δ6.66, which was assigned to H-3, was a quartet with a coupling constant of less than 1 Hz. Consequently the three-proton singlet at δ2.64, assigned to the C-4 methyl group, appeared as a doublet with a similar coupling constant. The other C-2 methyl group resonated as a singlet at δ2.54. It can therefore be inferred that the C3-C4 bond of the imidazo[1,5-a]-pyrimidine bicycle shows some double-bond character under the influence of the bridgehead nitrogen atom and this behaviour later became a useful tool to help assign the structures of imidazo[1,5-a]pyrimidines derived from ambiguous cyclisations. When the ^{1}H n.m.r. spectrum of the compound (402a) was run in $CDCl_3$ the C-2 methyl resonance appeared downfield of the C-4

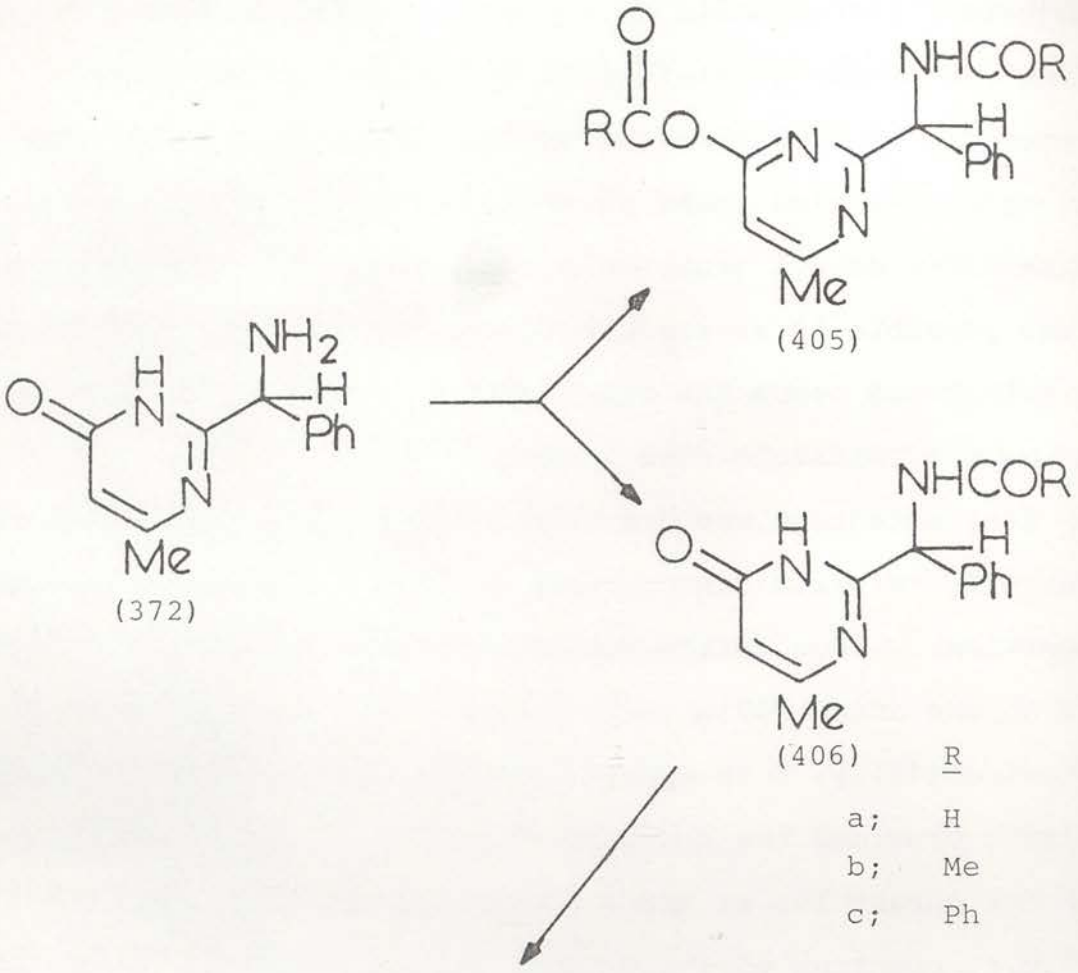
methyl resonance whereas conversely the opposite was observed when the spectrum was run in $(CD_3)_2SO$ and therefore although the C-4 methyl group might have been expected to be the more deshielded of the two methyl groups (as a consequence of being on a carbon atom α to an electron-deficient bridgehead nitrogen atom) it appeared that no assignment of the methyl groups could be made on the basis of their relative chemical shifts. In an identical manner (Scheme 100) the amines (371b) and (371c) were converted into the formamides (399b) and (399c) whose properties were fully consistent with their expected structures and in each case the product was obtained in about 50% yield. In the former reaction a by-product was also obtained in about 50% yield and identified as the formate salt of the amine (371b). Chlorinative cyclisation of the amide (399c) was straightforward and provided 8-phenylimidazo[1,5-a]pyrimidine (402c), in excellent yield, which was fully characterised. In contrast the unsymmetrical formamide (399b) gave a two component mixture explicable by cyclisation of the imidazole through both N-1 and N-3 of the pyrimidine ring. Both components were isolated and shown to give analytical data in accord with the molecular formula $C_{13}H_{11}N_3$ (m/e 209). The ^1H n.m.r. spectrum of the major component exhibited a doublet at δ7.98 coupled to a doublet δ6.40 attributable to H-4 and H-3 respectively while a three-proton singlet at δ2.55 was attributed to a methyl group at C-2 and the compound was assigned the 2-methyl-8-phenyl-imidazo[1,5-a]pyrimidine structure (402b) derived from cyclisation through N-1. The minor component was therefore assigned the isomeric structure (402d) derived from the alternative mode of cyclisation (through N-3) and the low yield of this compound

can be accounted for in terms of steric inhibition to the approach of the entering side-chain to N-3 by the adjacent methyl group. Further support for these assignments was obtained by the appearance in the ^{1}H n.m.r. spectrum of the isomer (402b) of a three-proton doublet at δ2.58 coupled to a one-proton doublet of quartets at δ6.40 in turn coupled to a one-proton doublet at δ8.16 attributable to the C-4 methyl group, H-3 and H-2 respectively.

The successful synthesis of the imidazo[1,5-a]pyrimidine nucleus via the projected synthetic route suggests that this sequence is particularly amenable for the preparation of such imidazopyrimidines containing a wide variety of substituents at the 6-position and it was therefore of interest to investigate the range of substituents which might be thus incorporated. Hence with the object in mind of preparing a 6-alkyl substituted imidazo[1,5-a]pyrimidine (Scheme 100) the amine (371a) was reacted with acetyl chloride in the presence of triethylamine to afford a good yield of the acetamide (400a) whose analytical and spectroscopic properties were fully consistent with the expected structure. Of particular relevance was the absorption at 1650 cm^{-1} in its i.r. spectrum attributable to the amide carbonyl and the display in its ^{1}H n.m.r. spectrum of a three-proton singlet at δ2.06 assigned to the acetamide methyl group. Cyclisation of the acetamide (400a) occurred smoothly (although more slowly than in the corresponding formamide case) to give a good yield of the trimethyl imidazo[1,5-a]pyrimidine (403a) and analytical data agreed with the anticipated product molecular formula $C_{15}H_{15}N_3$. The ^{1}H n.m.r. spectrum of this compound (403a) showed three methyl resonances and the C-4 methyl was

immediately recognisable by its appearance as a doublet coupled to the one-proton quartet at δ5.98 (attributed to H-3). Furthermore by comparison of the two remaining three-proton singlet resonances with other examples of this ring system containing either a C-2 methyl group or a C-6 methyl group, but not both, it was possible to assign the methyl resonance at δ2.38 to the C-2 methyl and hence the other methyl resonance at δ2.85 to that on the imidazole ring (C-6).

Next attention was directed towards the preparation of the imidazo[1,5-a]pyrimidine nucleus bearing an aryl group at the 6-position. Thus triethylamine-catalysed condensation (Scheme 100) of the amine (371a) with benzoyl chloride afforded the benzamide (401a). In accord with the structure (401a) elemental analysis provided the molecular formula $C_{20}H_{19}N_3O$ in agreement with the parent ion at m/e 317 shown in the mass spectrum. The ^1H n.m.r. spectrum of the product (401a) confirmed the presence of two phenyl groups and the benzylic proton appeared as a doublet at δ6.37 coupled to the amide NH proton observed as a doublet at δ8.31. The benzamides (401b) and (401c) were obtained by similar reaction of the amines (371b) and (371c) respectively and both showed analytical and spectroscopic data fully in accord with their structures. Subsequent cyclisation of all three benzamides (401a-c) was accomplished by heating with phosphoryl chloride. However whereas the benzamides (401a) and (401c) cyclised in a straightforward manner to provide the 6,8-diphenylimidazo[1,5-a]pyrimidines (404a) and (404c) respectively (and whose properties are consistent with these structures) the cyclisation of the benzamide (401b) was not so simple. The product of this cyclisation was a yellow solid which appeared to be t.l.c. pure and whose combustion analysis

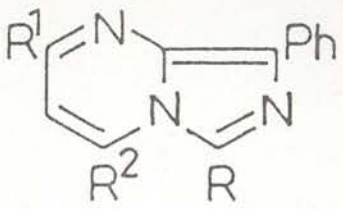


(372)

(405)

(406)

	R
a;	H
b;	Me
c;	Ph



(407)

	R	R^1	R^2
a;	H	Cl	Me
b;	H	Me	Cl
c;	Me	Cl	Me
d;	Me	Me	Cl
e;	Ph	Cl	Me
f;	Ph	Me	Cl

Scheme 101

provided the molecular formula $C_{19}H_{15}N_3$ agreeing with the parent ion exhibited in the mass spectrum at m/e 285. Moreover the i.r. spectrum of the substance showed the absence of any functional grouping, in particular the amide carbonyl and NH of the benzamide starting material (401b), thus suggesting that cyclisation had occurred. However the ^1H n.m.r. spectrum of the material showed that the solid was in fact a mixture of the diphenylimidazo[1,5-a]pyrimidines (404b) and (404d) with the less sterically-strained 2-methyl isomer (404b) dominating in the ratio 2:1.

It should be noted that as the size of the amide substituent increases (H to Me to Ph) correspondingly the cyclisation to give an imidazo[1,5-a]pyrimidine bearing that group at the 6-position becomes more difficult (as measured by the decrease in the yield of product obtained and a corresponding increase in the amount of starting material recovered). Furthermore for a particular C-6 substituent as the size of the group at C-4 increases (H to Me) the cyclisation is also retarded. When the cyclisation can give two products, whilst both are obtained, the product with the smaller group at C-4 predominates. These observations can be explained on the basis of peri-interactions[157,158] between the C-4 and C-6 groups.

As formation of 6-substituted imidazo[1,5-a]pyrimidines from the aminoalkylpyrimidines (371a-c) had been achieved it was of interest to extend this sequence to the aminoalkylpyrimidinone (372) whose synthesis has already been described (see Section 3.2). Thus on heating with formic acid (Scheme 101) the amine (372) was converted into the formamide (406a) whose analytical properties are consistent with its structure.

The i.r. spectrum of the compound (406a) shows only one absorption in the carbonyl region (1680 cm^{-1}) however the presence of a formamidobenzyl side chain was established by the appearance in its ^1H n.m.r. spectrum of a one-proton doublet at δ5.94 coupled to another one proton doublet at δ9.05 (attributable to the benzylic CH and the amide NH). Evidently, as the formyl proton appeared as a sharp singlet at δ8.14, no coupling of the amide NH and the formyl proton occurs. Cyclisation of the formamide (406a) was effected (Scheme 101) in phosphoryl chloride-1,2-dichloroethane to give a complex gum from which the only material isolated was a yellow solid obtained in 21% yield. Elemental analysis of this substance provided the molecular formula $C_{15}H_{10}ClN_3$ and its mass spectrum exhibited a parent ion distribution of 245/243 indicative of a monochloro-containing compound. That cyclisation had occurred was supported by the absence of any absorption in the i.r. spectrum of the product attributable to the amide side-chain of the starting material and therefore it was likely that the compound was either imidazo[1,5-a]pyrimidine (407a) or (407b) derived from cyclisation through N-1 or N-3. Clearly concomitant chlorination of the ring lactam had occurred at the cyclisation stage. The structure of this product was established by the appearance in its ^1H n.m.r. spectrum of a three-proton doublet at δ2.54 coupled to a one-proton quarter at δ6.40 with a coupling constant of about 1 Hz. This feature is attributable to a methyl group at C-4 coupled to a proton at C-3 and therefore allows assignment of the 2-chloro-4-methylimidazopyrimidine structure (407a) to this compound.

The amine (372) was next acetylated by direct reaction

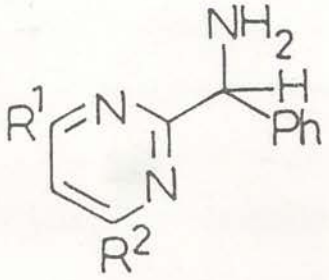
with acetyl chloride to give the acetamide (406b) although only in poor yield (37%). An attempt to catalyse this reaction with triethylamine produced a mixture of the desired acetamide (406b) and a second compound which exhibited a carbonyl absorption at 1745 cm^{-1}. Although it was not possible to separate this mixture, by analogy with the benzamide case, (see later) the ester-type carbonyl containing compound is thought to have the bis-acetylated structure (405b). Furthermore it was found that when the amine (372) was heated with acetic acid an excellent yield of the acetamide (406b) was obtained.

On chlorinative cyclisation the acetamide (406b) was converted into a two-component mixture which was subsequently separated by flash chromatography. Both compounds gave combustion analysis data consistent with the molecular formula $C_{14}H_{12}ClN_3$ and the mass spectrum of each showed a parent ion distribution of 259/257 thus demonstrating that both compounds contained one chlorine atom. In its ^1H n.m.r. spectrum the minor component exhibited a three-proton singlet at δ2.96 attributed to the C-6 methyl group as well as another three-proton singlet at δ2.42 for the methyl group on the pyrimidine ring. The proton at C-3 also resonated as a singlet thus showing that no coupling between it and the pyrimidine ring methyl occurred and hence allowing assignment of the 4-chloro-2-methylimidazopyrimidine structure (407d) to this compound. Consequently the major component was assigned the isomeric 2-chloro-4-methylimidazopyrimidine structure (407c) and confirmation of this assignment was obtained when the ^1H n.m.r. of the compound (407c) did show coupling between H-3 and the C-4 methyl group.

The amine (372) was also converted (Scheme 101) to the

benzamide (406c) in good yield although again the triethylamine catalysed condensation (with benzoyl chloride in this case) gave a minor product (6%). Elemental analysis and mass spectroscopy of the minor component agreed with the molecular formula $C_{26}H_{21}N_3O_3$ corresponding to a bis-benzoylated derivative and its ^1H n.m.r. spectrum confirmed the presence of three phenyl groups. The two doublets at δ6.38 and δ9.24 were assigned to the benzylic proton and the amide NH respectively thus confirming that the amino-function was not bis-acylated and therefore the remaining position available for acylation was the lactam unit. The i.r. spectrum of the compound showed carbonyl absorptions at both 1655 cm^{-1} (for the amide side-chain) and 1745 cm^{-1}. The higher carbonyl absorption can be attributed to an O-benzoyl grouping and the by-product is therefore assigned the structure (405c). An alternative site for the second acylation could be the lactam N-atom however this possibility was rejected on the basis that the i.r. spectrum of such a compound would contain three carbonyl absorptions none of which should appear at as high a frequency as 1745 cm^{-1}. On cyclisation the benzamide (406c) was converted into an isomeric mixture of the two possible products (407e) and (407f) in the ratio 3:1. The isomers could not be separated chromatographically but the mixture analysed for the molecular formula $C_{19}H_{14}ClN_3$ and its ^1H n.m.r. spectrum confirmed the presence of both isomers (407e) and (407f).

To extend this synthetic sequence it was decided to attempt the preparation of the imidazo[1,5-a]pyrimidine nucleus containing an amine group at the 6-position. Thus it was hoped that the foregoing strategy of acylation of the aminobenzyl group and subsequent cyclisation of the resulting amide could be modified

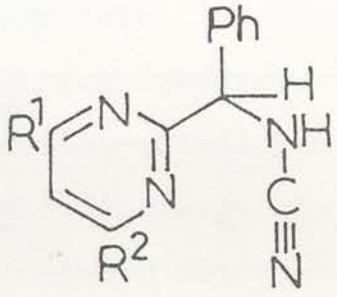


(371)

	R^1	R^2
a;	Me	Me
b;	Me	H
c;	H	H

(i) (ii)

(408)

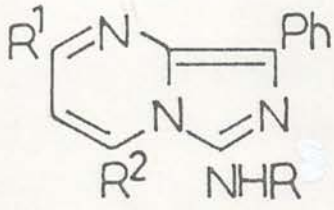


(409)

	R^1	R^2
a;	Me	Me
b;	Me	H
c;	H	H

(iii)

	R	R^1	R^2
a;	Me	Me	Me
b;	Ph	Me	Me
c;	H	Me	Me
d;	H	H	H



(410)

(i) R NCO

(ii) BrCN

(iii) $POCl_3$

Scheme 102

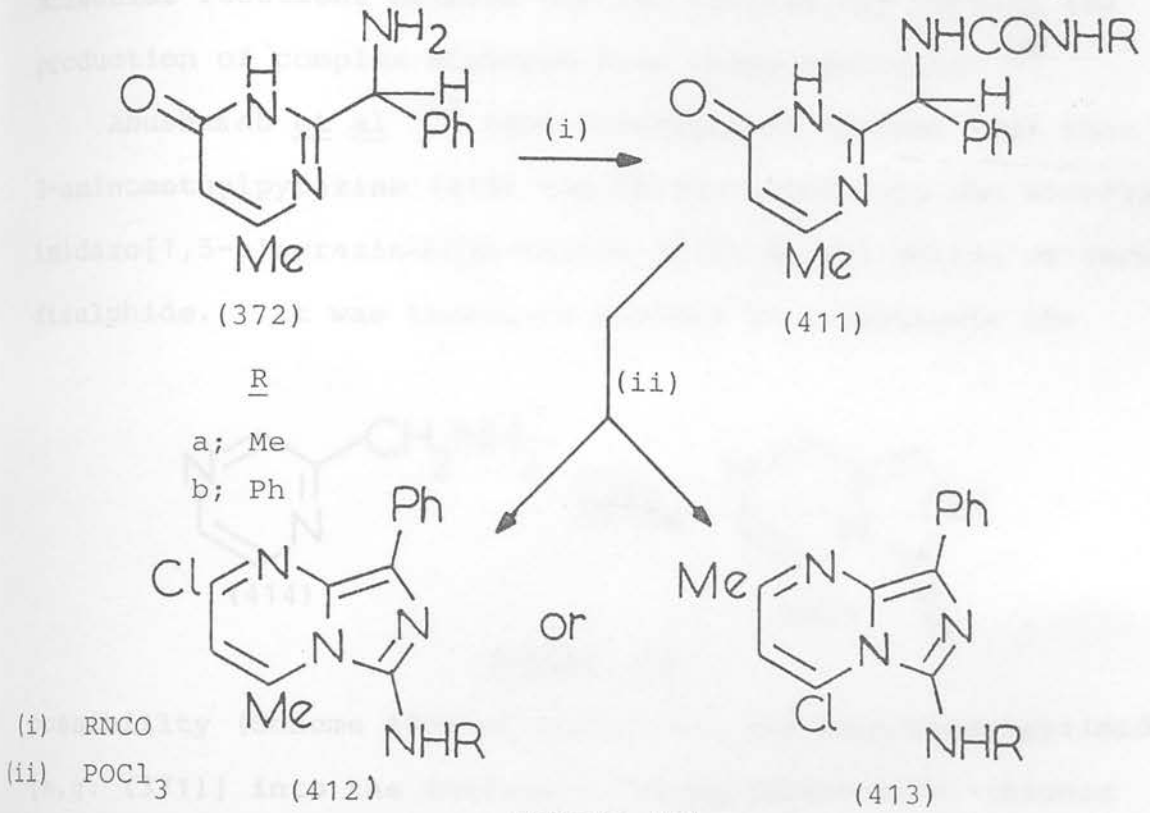
by reaction of the aminoalkyl pyrimidines with isocyanates to give urea intermediates [e.g. Scheme 102; (408)]. Such urea derivatives might also be amenable to cyclisation on treatment with phosphoryl chloride to provide the 6-substituted-amino-imidazo[1,5-a]pyrimidines (410). To this end the amine (371a) was reacted with methyl isocyanate (Scheme 102) whence a colourless solid was deposited from solution in good yield. The i.r. spectrum of this material showed various absorptions in the NH region (3345-3320 cm^{-1}) as well as an absorption at 1630 cm^{-1} assigned to the urea carbonyl. Analytical data provided the molecular formula $C_{15}H_{18}N_4O$ (m/e 270). The assignment of the urea structure (408a) to this compound was supported by the ^1H n.m.r. spectrum of the product which contained a three-proton doublet at δ2.68 coupled to a one-proton doublet at δ6.07 attributable to the urea NHMe moiety. Subsequently the urea (408a) was heated in phosphoryl chloride-1,2-dichloroethane whereupon ring closure occurred rapidly to give a quantitative yield of the bright red 6-methylamino-imidazo[1,5-a]pyrimidine (410a). Accordingly elemental analysis of this compound confirmed the molecular formula $C_{15}H_{16}N_4$ and the mass spectrum exhibited a parent ion at m/e 252. Moreover the ^1H n.m.r. spectrum of the compound (410a) showed the presence of three methyl groups and in particular demonstrated that the initially equivalent pyrimidine methyl groups appeared as two separate resonances confirming that cyclisation had indeed occurred. Furthermore the observed ease of cyclisation of the urea (408a) implies that the insertion of an NH moiety between C-6 and the methyl group relieves the steric strain imposed by peri-interactions.

Extension of this strategy (Scheme 102) to the preparation of a 6-arylamino derivative of the imidazo[1,5-a]pyrimidine ring system was accomplished by similar reaction of the amine (371a) with phenyl isocyanate to afford the phenylurea (408b). When heated with phosphoryl chloride in 1,2-dichloroethane the urea (408b) cyclised rapidly to provide an excellent yield of the 6-anilino-imidazopyrimidine (410b) and both the cyclic product and its precursor showed spectroscopic and analytical properties entirely consistent with their assigned structures.

Following the successful preparation of the imidazo[1,5-a]-pyrimidine ring system containing a substituted-amino group in the 6-position it was of interest to attempt the preparation of the corresponding primary amine. A possible synthesis of such a bicyclic amine [i.e. Scheme 102; (410c)] would involve the conversion of the aminoalkylpyrimidine (371a) into the urea (408c) and thence via phosphoryl chloride cyclisation to the desired product (410c). However it was considered that the monocyclic amine (371a) might be converted directly into the bicyclic amine (410c) and when a solution of the former was treated with cyanogen bromide an orange solid was precipitated. The ^{1}H n.m.r. spectrum of the solid contained a three-proton singlet at δ2.36 and a three-proton doublet at δ2.76 coupled to a one-proton quartet at δ6.44 thereby confirming that cyclisation had occurred and elemental analysis provided the molecular formula $C_{14}H_{15}BrN_4$ (M, 319). In contradiction the mass spectrum recorded the parent ion at m/e 238 and the discrepancy of 81 mass units can be attributed to HBr hence allowing the structure of the compound to be assigned as the hydrobromide salt of the desired amino-compound (410c) (Scheme 102). Work-

up of the mother liquor provided a small amount of solid which was identical to the product obtained on repetition of the reaction with basification of the reaction mixture during work-up. As expected this solid gave analytical and spectroscopic data entirely consistent with the free amine (410c). In a similar fashion (Scheme 102) the amine (371c) was converted into the bicyclic product, 6-amino-8-phenylimidazo[1,5-a]-pyrimidine (410d) and this compound was also fully characterised. The mechanism of these reactions is thought to involve amino-N-cyano intermediates [e.g. Scheme 102; (409a) and (409c)] which spontaneously cyclise to the desired amino-compounds [(410c) and (410d)].

Again it was of interest to examine the possibility of extending these aminative cyclisations to the aminobenzylpyrimidinone (372) (Scheme 103). With this objective in mind the amine (372) was reacted with methyl isocyanate to afford a good yield of the colourless methylurea (411a) whose analytical and spectroscopic properties were fully in accord with the assigned structure. Attempted chlorinative cyclisation of the urea (411a) produced only a crimson coloured multicomponent gum. A trace amount of solid isolated gave a mass spectrum parent ion at m/e 274/272 corresponding to either of the isomeric products (412a) or (413a) however elemental analysis of this material produced only spurious results. The amine (372) was also reacted with phenyl isocyanate (Scheme 103) to provide a good yield of a colourless product which was identified as the phenylurea (411b) by the appearance of a parent ion in the mass spectrum of the compound at m/e 334. Moreover support for the urea structure (411b) was obtained from the ^{1}H n.m.r. spectrum of the substance which

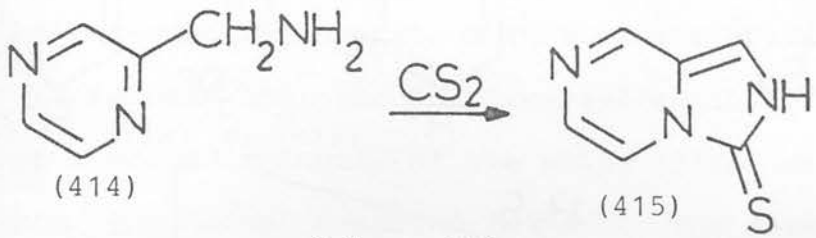


Scheme 103

demonstrated the presence of two phenyl groups and showed that the benzylic proton, which resonated as a doublet at δ5.80 was coupled to a single NH. Satisfactory elemental analysis could not however be obtained from this compound and therefore the structure assignment of the urea (411b) must be tentative. Subsequent treatment of this compound with phosphoryl chloride with a view to obtaining the chlorinated aniline derivatives (412b) and (413b) produced a multicomponent mixture. The failure of these reactions to provide the substituted-amino derivatives (412) and (413) is thought to be a consequence of the concomitant chlorination of the pyrimidinone lactam unit during the cyclisation procedure. Such chlorination would afford the expected products (412) and (413) containing both an electrophilic function (-Cl) and a nucleophilic function (-NHR) and inter-

molecular reactions between the two centres may explain the production of complex mixtures from these reactions.

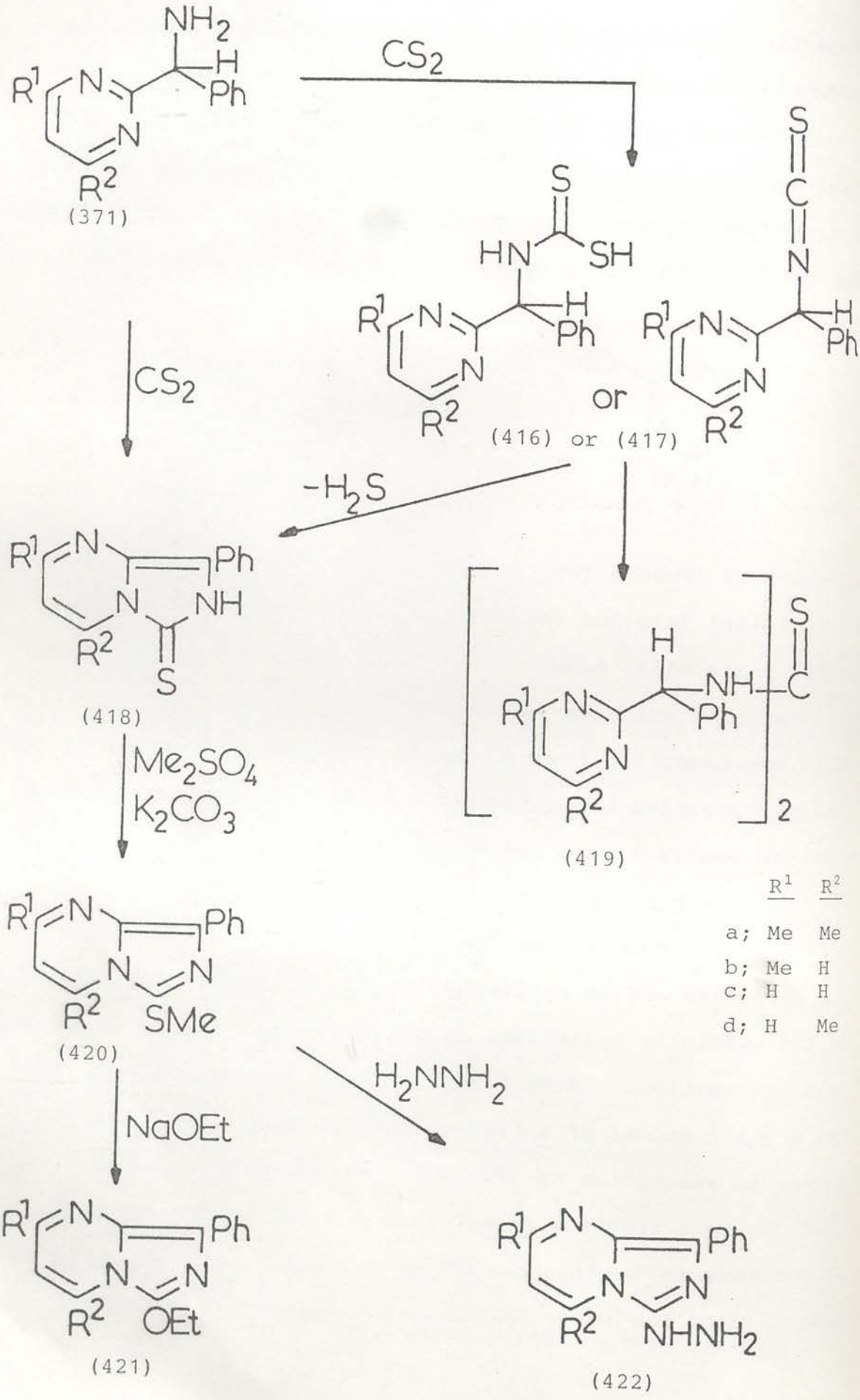
Abushanab *et al* [138] have demonstrated (Scheme 104) that 2-aminomethylpyrazine (414) can be converted into the bicyclic imidazo[1,5-a]pyrazin-6(7H)-thione (415) by the action of carbon disulphide. It was therefore decided to investigate the



(414) (415)

Scheme 104

possibility (Scheme 105) of converting the aminobenzylpyrimidines [e.g. (371)] into the imidazo[1,5-a]pyrimidin-6(7H)-thiones (418) in a similar manner. Thus the amine (371a) was heated with carbon disulphide in toluene and a bright red crystalline solid was deposited from solution. Elemental analysis of this material provided the molecular formula $C_{14}H_{13}N_3S$ in agreement with the observed mass spectrum parent ion at m/e 155 thus allowing the thione structure (418a) to be assigned to the compound. The ^1H n.m.r. spectrum of the thione (418a) was consistent with its structure and in particular demonstrated the differentiation of the initially equivalent pyrimidine methyl groups which occurs upon cyclisation. Also formed in this reaction (Scheme 105) was a small amount of a fawn by-product whose i.r. spectrum showed an absorption at 3350 cm^{-1} attributable to an NH. Moreover the mass spectrum showed a parent ion at m/e 468 which corresponds to the thiourea (419a) derived from reaction of two molecules of the amine (371a) with one molecule of carbon



	R^1	R^2
a;	Me	Me
b;	Me	H
c;	H	H
d;	H	Me

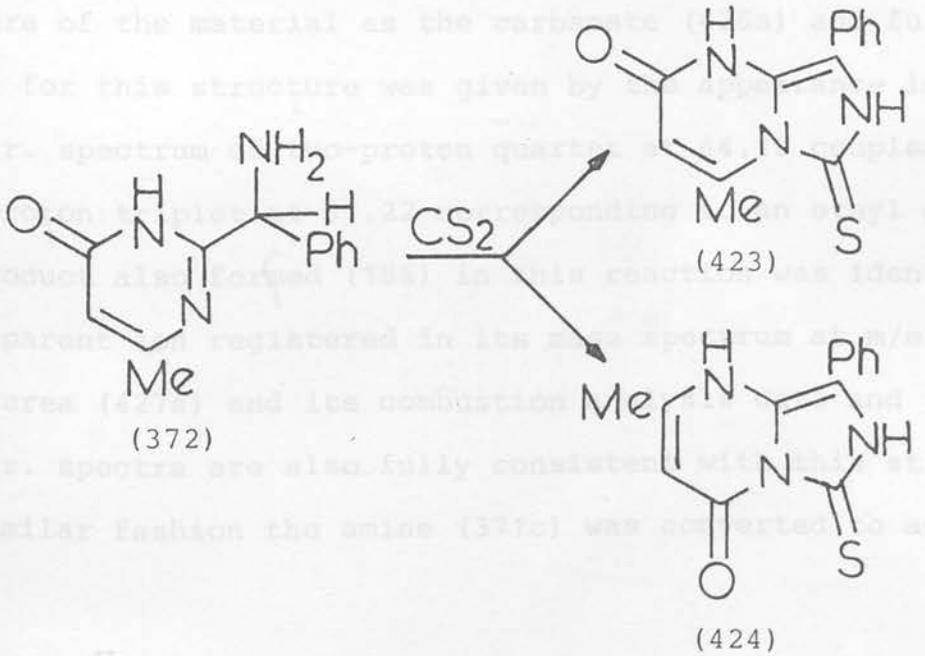
Scheme 105

disulphide. The mechanism of the cyclisation to the thione (418a) may involve an intermediate thiocarbamic acid such as (416a) or alternatively the reaction may proceed through the isothiocyanate compound (417a). Evidence that the latter sequence is in operation was obtained when the analogous thione (418c) was prepared by treatment of a BF_3-triazolo[1,5-a]-pyrimidine complex with sodium thiocyanate (see Chapter 2) wherein the intermediate must be a thiocyanate species. Consequently it appears that the thiourea (419a) is formed from reaction of a second molecule of the amine (371a) with the intermediate isothiocyanate compound (417a). The amines (371b) and (371c) were also treated with carbon disulphide (Scheme 105) under the same conditions to afford the imidazopyrimidine-thiones (418b) and (418c) respectively both of which gave analytical and spectroscopic data consistent with the assigned structures. Of special relevance is the observation that the amine (371b) was converted only into the 2-methylimidazo-pyrimidine-thione (418b), none of the isomeric 4-methyl compound (418d) being observed. This is explicable in terms of steric repulsion between the C=S moiety and the methyl group diverting the reaction to the alternative mode of cyclisation.

It has also been demonstrated[138] (Scheme 105) that thiones of the type (418) can be S-methylated and therefore attention was directed to the aim of investigating the preparation and reactivity of such thiomethyl compounds [e.g. (420)] to nucleophilic displacement. Thus treatment of the imidazo[1,5-a]-pyrimidin-6(7H)-thione (418a) with dimethyl sulphate and potassium carbonate gave an excellent yield of an orange product which analysed for the molecular formula $C_{15}H_{13}N_3S$ and exhibited a

parent ion at m/e 269 in its mass spectrum. Confirmation that methylation had occurred was given by the ^{1}H n.m.r. spectrum of the product which contained three resonances attributable to methyl groups. As usual the C-4 methyl group was instantly recognisable due to its appearance as a doublet at δ2.80 (coupled to H-3) and the remaining two three-proton singlets at δ2.69 and δ2.39 were tentatively assigned to the S-methyl and the C-2 methyl respectively. The assignment of the thiomethyl structure (420a) to this compound is made by analogy with the work of Abushanab et al [138] but the alternative N-methylated compound cannot be rigorously excluded. The thiomethyl compound (420a) however failed to react with either sodium ethoxide or hydrazine to give the derivatives (421a) and (422a) respectively, in each case the thiomethylimidazopyrimidine (420a) being recovered unchanged.

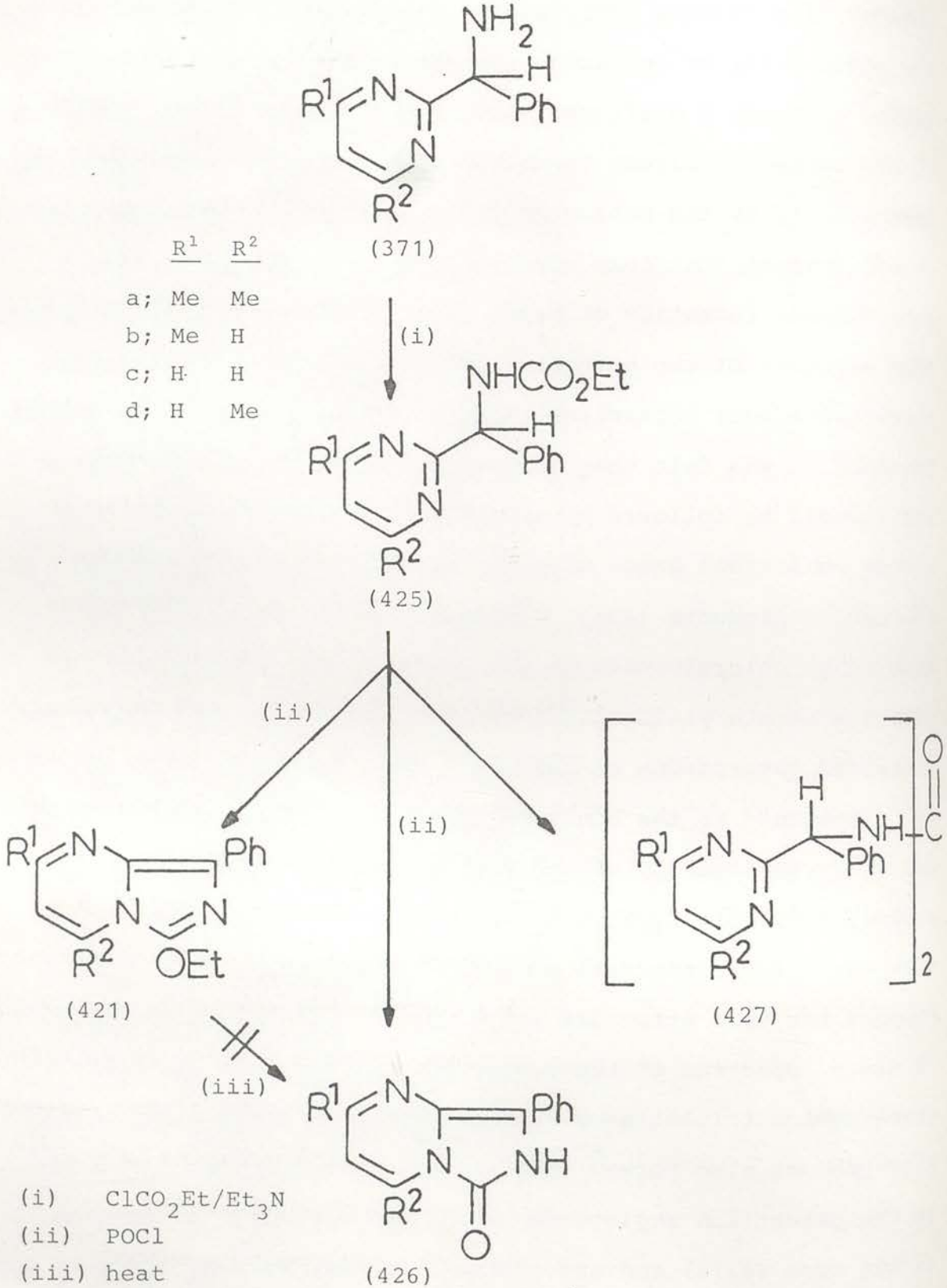
An attempt to extend the foregoing sequence to the preparation of the imidazo[1,5-a]pyrimidinone-thiones (423) and (424) by a similar reaction of the pyrimidinone-amine (372) gave only a complex solid which decomposed rapidly in solution.



(372) (423) (424)

Scheme 106

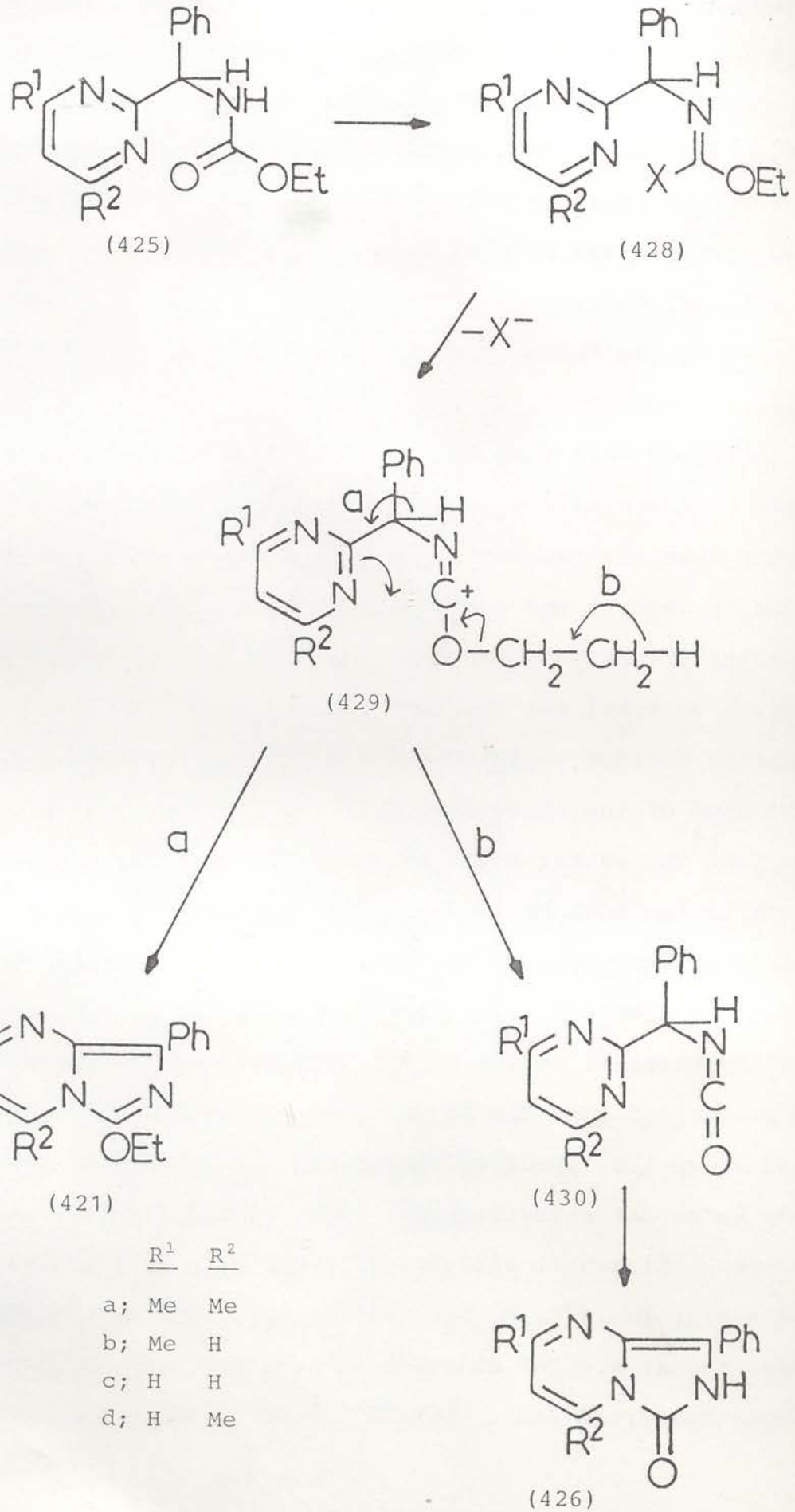
The preparation of the imidazo[1,5-a]pyrimidin-6(7H)-thiones [i.e. Scheme 105; (418)] suggested an investigation into the possibility of preparing the oxo-analogues [i.e. Scheme 107; (426)] although a different route was required in the synthesis of the latter. Direct formation of the ketones (426) from the amines (371) by the action of phosgene might be possible however it was thought that this approach might be plagued by the simultaneous formation of ureas [i.e. Scheme 107; (427)] derived from reaction of two molecules of the amine with phosgene and therefore a more controlled entry to these compounds was sought. Moreover it was felt that initial formation of the carbamates (425) could be followed by elimination of ethanol under more severe conditions hence allowing the reaction to be directed to the cyclic products (426). Thus the amine (371a) was reacted with ethyl chloroformate in the presence of triethylamine to give a moderate yield of colourless solid whose i.r. spectrum contained absorptions at 3290 cm^{-1} (attributable to NH) and 1720 cm^{-1} (assigned to the urethane carbonyl). Elemental analysis and mass spectroscopy of the product were in accord with the molecular formula $C_{16}H_{19}N_3O_2$ (m/e 285) thus confirming the structure of the material as the carbamate (425a) and further support for this structure was given by the appearance in its ^1H n.m.r. spectrum of two-proton quartet at δ4.10 coupled to a three-proton triplet at δ1.22 corresponding to an ethyl group. A by-product also formed (18%) in this reaction was identified, by the parent ion registered in its mass spectrum at m/e 452, as the urea (427a) and its combustion analysis data and i.r. and ^1H n.m.r. spectra are also fully consistent with this structure. In a similar fashion the amine (371c) was converted to an


NH2
H
Ph
R1
N
N
R2
(371)
R1 R2
a; Me Me
b; Me H
c; H H
d; H Me
(i)
NHCO2Et
H
Ph
(425)
(ii)
(ii)
(ii)
Ph
OEt
(421)
(iii)
(426)
O
C
NH
2
(427)
(i) ClCO2Et/Et3N
(ii) POCl
(iii) heat

Scheme 107

intermediate carbamate (425c) whose spectroscopic and analytical properties are in accord with the assigned structure, although none of the by-product urea (427c) was isolated in this case. In both the above reactions the yield of the desired carbamates (425) was increased substantially when the amount of triethylamine catalyst was reduced from 2.5 equivalents to 1 equivalent and this may suggest that the formation of the by-product (427) isolated in the former case is assisted by the excess triethylamine.

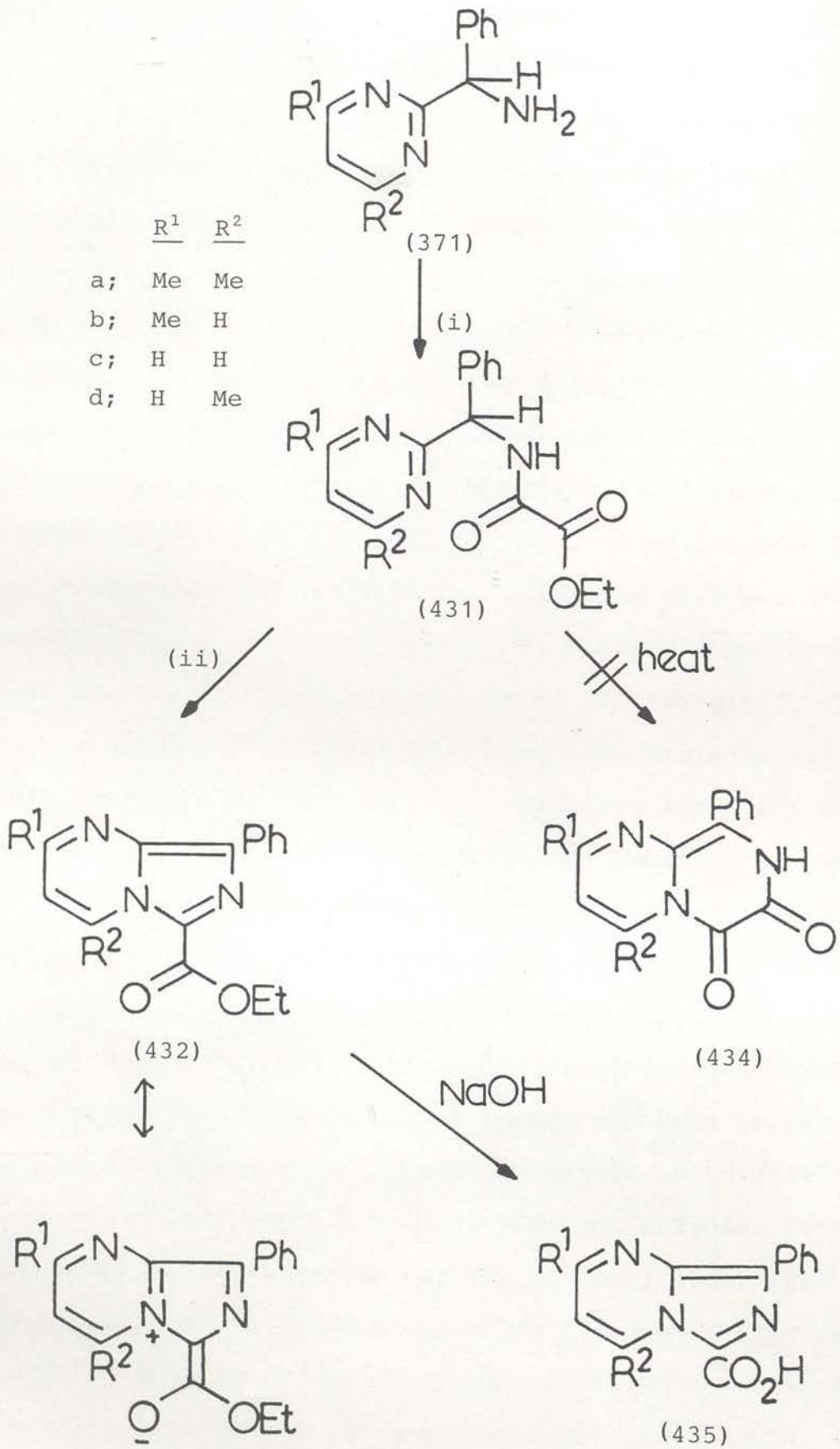
Attempts were then made (Scheme 107) to convert the carbamate (425a) to the cyclic urea (426a) under thermal conditions. However when the carbamate (425a) was heated under reflux in xylene or when it was subjected to dry heat in a Kugelrohr apparatus either under vacuum or at atmospheric pressure the starting material was recovered in excellent yield. It was therefore decided to attempt the previously unknown chlorinative conversion of the carbamates (425) to the ethers (421) in the hope that the latter might be amenable to de-alkylation to provide access to the ketones (426). Thus the carbamate (425a) was treated with phosphoryl chloride under the usual cyclisation conditions whence a three component mixture, containing unreacted starting material as one of the components, was produced. Of the two products formed the major compound was obtained as an orange solid whose i.r. spectrum registered the absence of any carbonyl group hence demonstrating that the urethane grouping was not present. Elemental analysis of this compound indicated the molecular formula $C_{16}H_{17}N_3O$ and the mass spectrum showed a parent ion at m/e 267 allowing the substance to be assigned the ether structure (421a). Confirmation of the structure (421a)



	R^1	R^2
a;	Me	Me
b;	Me	H
c;	H	H
d;	H	Me

Scheme 108

was provided by the exhibition in its ^1H n.m.r. spectrum of a normal triplet-quartet (expected for an ethoxy-group) and two separate resonances for the pyrimidine methyl groups indicative of cyclisation to a bicyclic compound. The minor component of this mixture was a red solid, containing an absorption at 1690 cm^{-1} in its i.r. spectrum attributable to an amide carbonyl, and for which elemental analysis and mass spectroscopy agreed on the molecular formula $C_{14}H_{13}N_3O$ (m/e 239). The ^1H n.m.r. spectrum of the by-product also showed two separate resonances for the pyrimidine methyl groups, the C-2 methyl group appearing as a singlet at δ2.21 while the C-4 methyl showed as a doublet at δ2.61 coupled to H-3, hence demonstrating that the minor component was also bicyclic. No resonances attributable to an ethyl group were registered and the compound was assigned the imidazo[1,5-a]pyrimidin-6(7H)-one structure (426a). An identical result was obtained on similar treatment of the carbamate (425c) and both the major component, the ether (421c), and the minor component, the ketone (426c) gave analytical and spectroscopic data entirely consistent with their assigned structures. The formation of the ketones (426) under these conditions was unexpected. Moreover when the ether (421c) was re-subjected to the chlorinating conditions no reaction was observed thus demonstrating that the ketone (426c) is not formed from the ether (421c) by de-alkylation under the conditions of cyclisation. Phosphoryl chloride cyclodehydration (Scheme 108) of molecules of the type (425) involves initial reaction of the amide-enol tautomer with phosphoryl chloride to give a phosphorus containing species (428; $X=OPOCl_2$). Under normal chlorinating conditions such an intermediate would decompose to the corresponding chloro-



(i) $ClCOCO_2Et/Et_3N$

(ii) $POCl_3$

Scheme 109

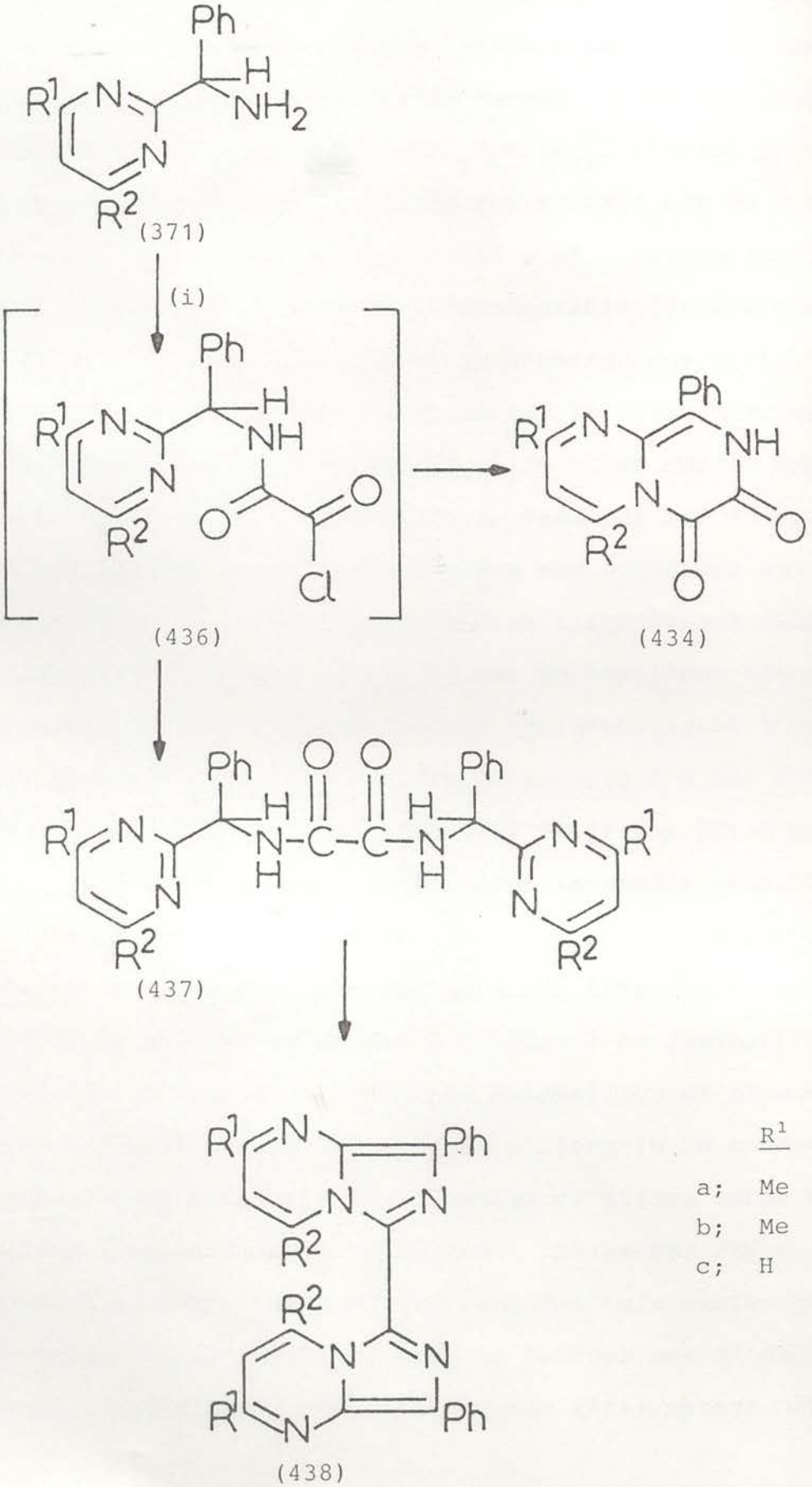
compound (428; X=Cl) and the departure of the chloride anion causes the formation of the carbonium ion (429). In this case however the attacking nucleophile is intermolecular and it is possible that it is the departure of the phosphorous moiety which provokes cyclisation. Competing loss of the benzylic proton and the most remote ethyl proton from the carbonium ion (429) would therefore account for the formation of both the ether (421) and an intermediate isocyanate compound (430) which would rapidly cyclise to the ketone (426). The absence of any cyclisation under thermal conditions precludes a similar competitive loss of OH or OEt in the carbamate tautomer (428; X=OH).

The successful synthesis of the ketones (426) demonstrated the scope of the acylation-cyclisation strategy as applied to the 2-aminoalkylpyrimidines [i.e. Scheme 107; (371)] and it was therefore of interest to extend this type of sequence to other acyl halides. Thus reaction of the amine (371a) with ethyl oxalyl chloride (Scheme 109) gave an almost quantitative yield of a fawn solid whose i.r. spectrum contained carbonyl absorptions at both 1700 cm^{-1} and 1755 cm^{-1} as well as absorption at 3340 cm^{-1} attributable to NH. Elemental analysis of the material provided the molecular formula $C_{17}H_{19}N_3O_3$ in agreement with the mass spectrum parent ion at m/e 313 and its ^1H n.m.r. spectrum exhibited a six-proton singlet at δ2.42 and a one-proton singlet at δ6.86 consistent with a mono-cyclic dimethylpyrimidine ring. Additionally the n.m.r. spectrum showed the benzylic proton as a doublet coupled to one NH proton, also shown as a doublet. A triplet-quartet indicated the presence of an ethyl group thus allowing the compound to be assigned the oxamate structure (431a). Analogous reaction of the amines (371b) and (371c)

with ethyl oxalyl chloride provided the oxamates (431b) and (431c) both of whose analytical and spectroscopic properties were in line with their assigned structures. On treatment of the oxamate (431a) under chlorinative cyclisation conditions with prolonged heating (68 h) a yellow product was isolated whose i.r. spectrum showed no amide absorptions but did exhibit a carbonyl absorption at 1710 cm^{-1}. The mass spectrum parent ion indicated a molecular weight of 295 and combustion analysis provided the molecular formula $C_{17}H_{17}N_3O_2$. The ^1H n.m.r. spectrum of the product showed the pyrimidine methyl groups to be non-equivalent, thus demonstrating that cyclisation had occurred, and the presence of a three-proton triplet at δ2.61 coupled to a two-proton quartet at δ4.61 suggested that the CO_2Et group remained intact. The compound was therefore assigned the 2,4-dimethyl-6-ethoxycarbonyl-8-phenylimidazo[1,5-a]pyrimidine structure (432a) and the carbonyl absorption at 1710 cm^{-1}, apparently attributable to the ester group, can be accounted for in terms of some conjugated amide character due to the charge separated resonance structure (433a). The oxamate (431c) also cyclised in an uncomplicated fashion to afford the 6-ethoxycarbonyl-substituted imidazopyrimidine (432c) whose i.r. spectrum showed a carbonyl absorption at 1690 cm^{-1}, again due to contribution from the resonance structure (433c), and whose ^1H n.m.r. spectrum and combustion analysis are consistent with the assigned structure. However, as had been found in previous cyclisation reactions of derivatives of the amine (371b), the oxamate (431b) did not cyclise in a straightforward manner because of the ambiguity created by the unsymmetrically substituted pyrimidine ring. Thus the cyclisation in this case gave a good yield of

yellow solid which was shown by ^{1}H n.m.r. spectroscopy to be a mixture of the two possible products (432b) and (432d) in the ratio 2:1. The isomeric mixture could not be separated chromatographically however elemental analysis provided the molecular formula $C_{16}H_{15}N_3O_2$ and the parent ion in the mass spectrum of the mixture was exhibited at m/e 281 in accord with either structure. As a further proof of the structure of the 6-ethoxycarbonylimidazopyrimidines [i.e. Scheme 109; (432)] the ester (432c) was heated with 2M aqueous sodium hydroxide when an excellent yield of yellow solid was deposited. The i.r. spectrum of the solid still contained a carbonyl absorption (1690 cm^{-1}) and the mass spectrum showed a parent ion at m/e 239 hence the substance was assigned the 8-phenylimidazo[1,5-a]-pyrimidin-6-carboxylic acid structure (435c). The acid structure (435c) was confirmed by its ^{1}H n.m.r. spectrum which displayed a trio of double-doublets attributable to the ABX system of the H-2, H-3 and H-4 protons as well as a very broad resonance between δ6.75 and δ9.00 assigned to the acid proton. However satisfactory elemental analysis data could not be obtained for this product.

Having prepared the oxamates [i.e. Scheme 109; (431)] it was of interest to investigate the possibility that they might be amenable to cyclisation to form the 6-6 system (434) by thermal elimination of ethanol. To this end the oxamate (431c) was heated under reflux in xylene however only unreacted starting material was recovered. Furthermore heating under reflux in dibenzyl ether also returned the unchanged oxamate (431c) and therefore it was decided to approach the preparation of the bicyclic system (434) via an alternative strategy. Consequently



	R^1	R^2
a;	Me	Me
b;	Me	H
c;	H	H

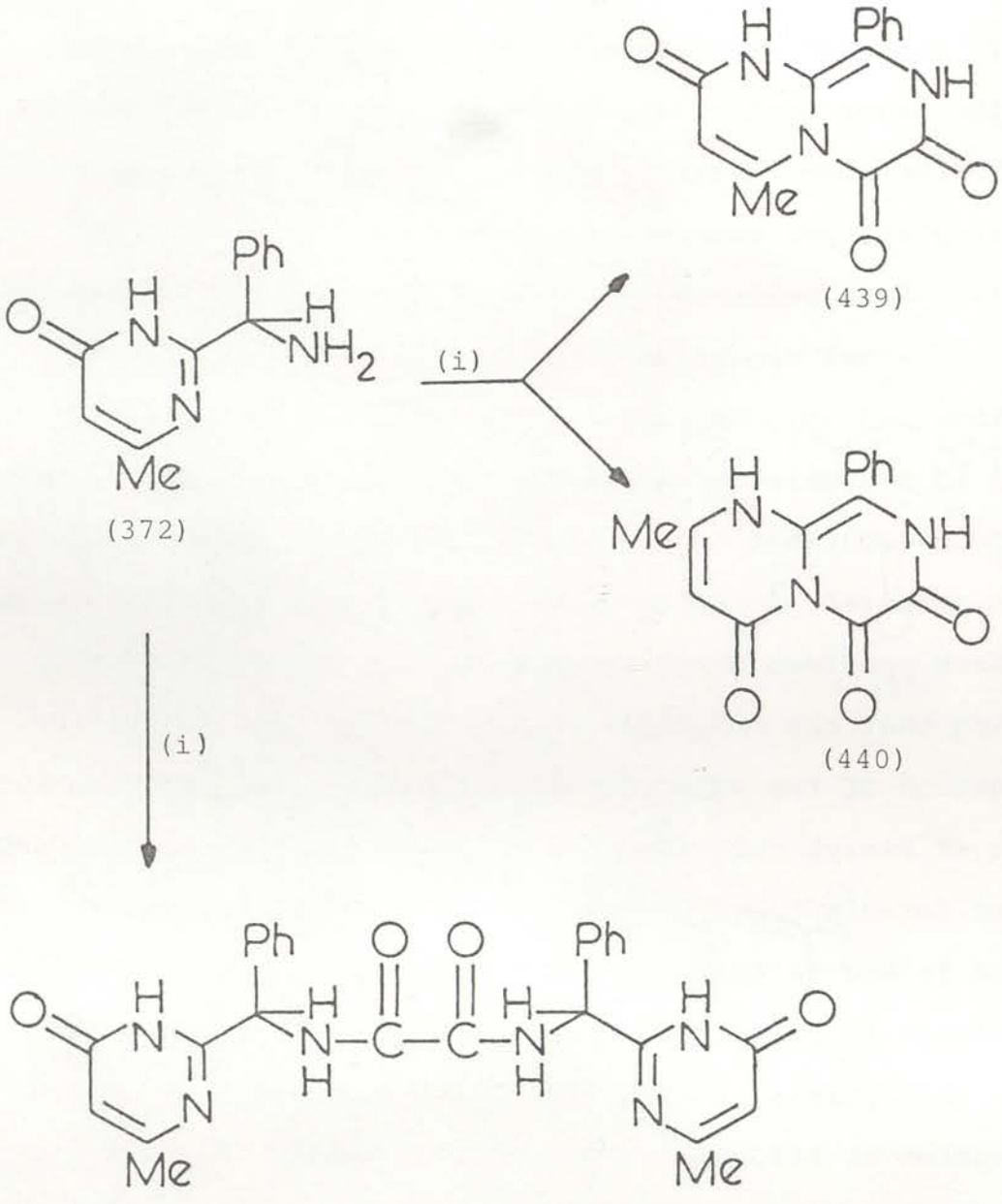
(i) $ClCOCOCl/Et_3N$

(ii) $POCl_3$

Scheme 110

the amine (371a) was treated (Scheme 110) with oxalyl chloride in the presence of one equivalent of triethylamine whereupon a crimson colour rapidly developed. Two products were isolated from this reaction, the minor product remaining in solution whilst the major product was deposited with the triethylamine hydrochloride also formed. The i.r. spectrum of the major component displayed absorptions at 3360 cm^{-1} and 1680 cm^{-1} indicative of an amide while its ^1H n.m.r. spectrum showed the pyrimidine methyl groups as a singlet hence suggesting that cyclisation had not occurred. However the benzylic proton appeared as a doublet at δ6.03 coupled to a one-proton doublet at δ9.29 attributable to a single NH demonstrating that acylation had been achieved. The structure of the substance was established by its mass spectrum which exhibited a parent ion at m/e 480 suggesting that the compound was the oxamide (437a) derived from reaction of two molecules of the amine (371a) with one molecule of oxalyl chloride. Elemental analysis supported the molecular formula $C_{28}H_{28}N_6O_2$ in accord with this structure.

Also formed in this reaction (Scheme 110) was a bright red solid (albeit in low yield) whose i.r. spectrum contained carbonyl absorptions at both 1650 and 1740 cm^{-1} as well as an NH absorption at 3140 cm^{-1}. That this compound was a bicycle was clearly demonstrated by its ^1H n.m.r. spectrum which showed the characteristic pattern of the C-2 methyl resonance as a singlet at δ2.16 and the C-4 methyl resonance as a doublet at δ2.69 coupled to H-3 which therefore resonated as a quartet at δ5.82. The spectrum also showed a phenyl group and a one-proton broad singlet at δ9.60-9.50 attributed to an NH and the compound was assigned the pyrazino[1,2-a]pyrimidine structure (434a).

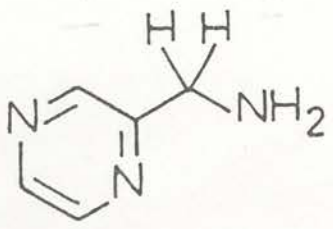


(i) $ClCOCOCl/Et_3N$

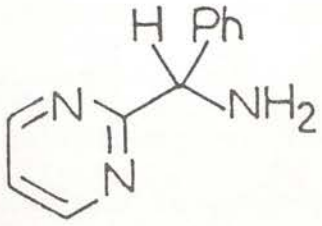
Scheme 111

Elemental analysis provided the molecular formula $C_{15}H_{13}N_3O_2$ and the mass spectrum supplied the molecular weight 267 in accord with this structure. Evidently the intermediate compound (436a) is attacked both intermolecularly and intramolecularly and the competition lies in favour of the latter mode to produce more of the oxamide (437a) than the bicyclic compound (434a). Repetition of the reaction with the amine (371c) with a view to reducing the steric hindrance to cyclisation by removing the pyrimidine methyl groups and hence promote bicycle formation gave a similar result. Thus the major component isolated was the oxamide (437c) while only a small amount of the pyrazinopyrimidine (434c) was obtained and both components showed analytical and spectroscopic properties consistent with their formulations.

Although the oxamides [Scheme 110; (437)] were obtained as unwanted by-products it appeared that their bis-amide structure might make them appropriate precursors to the bis-imidazo-[1,5-a]pyrimidines (438) via a dual cyclisation procedure. To investigate the possibility of performing such a tandem cyclisation the oxamide (437c) was heated with phosphoryl chloride-1,2-dichloroethane to give a high-melting orange solid whose i.r. spectrum showed the absence of the oxamide function. Moreover the mass spectrum of the substance exhibited a parent ion at m/e 388 indicating that a double dehydration had occurred and therefore the compound was formulated as the bis-imidazo-[1,5-a]pyrimidine (438c). However, the extreme insolubility of the compound (438c) prevented its ^1H n.m.r. spectrum being recorded and satisfactory combustion analysis data was not obtained for the same reason.



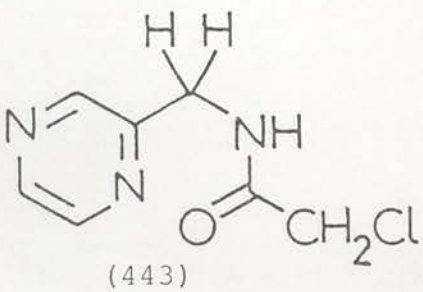
(442)



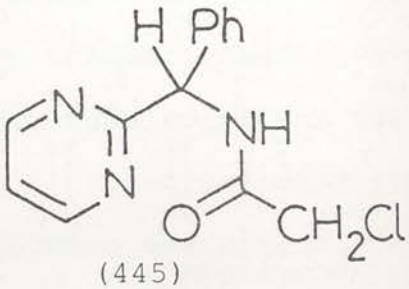
(371c)

(i)

(i)



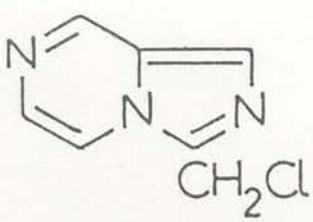
(443)



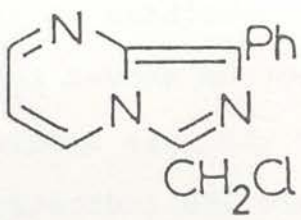
(445)

(ii)

(ii)



(444)



(446)

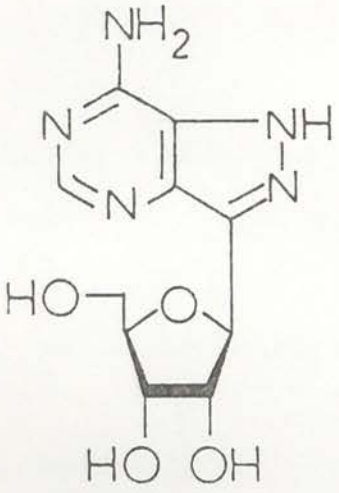
(i) $ClCOCH_2Cl/Et_3N$

(ii) $POCl_3$

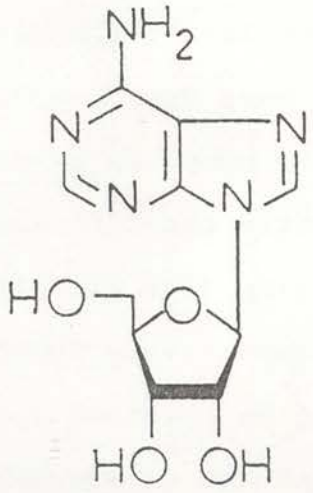
Scheme 112

An attempt was made (Scheme 111) to extend the synthesis of the pyrazino[1,2-a]pyrimidin-6,7-diones [i.e. Scheme 110; (434)] to the aminobenzylpyrimidinone (372) in the hope of isolating either of the isomeric triones (439) or (440). However when the amine (372) was treated with oxalyl chloride in the presence of triethylamine the only product isolated was a colourless solid whose mass spectrum displayed a parent ion at m/e 484 hence allowing the compound to be assigned the oxamide structure (441). Accordingly the i.r. spectrum of the oxamide showed absorptions at 3370, 1700 and 1660 cm^{-1} for the NH and both carbonyl types respectively however satisfactory analytical results could not be obtained for this compound.

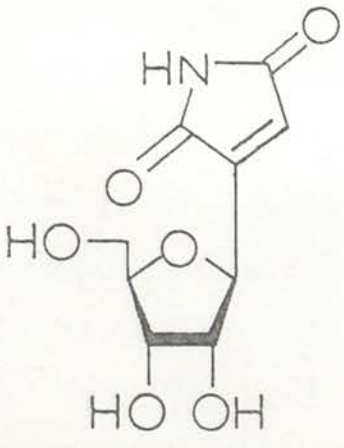
Abushanab and his co-workers[135] have demonstrated (Scheme 112) that the aminomethylpyrazine (442) reacts smoothly with chloroacetylchloride to afford the chloroacetamide (443) but that under phosphoryl chloride cyclisation conditions, designed to provide the 6-chloromethylimidazo[1,5-a]pyrazine (444), the latter compound was unstable and no product was isolated. It was therefore of interest to parallel these reactions in the pyrimidine series (Scheme 112) and thus the amine (371c) was treated with triethylamine and chloroacetyl chloride to give a good yield of colourless solid. Combustion analysis of the material gave the molecular formula $C_{13}H_{12}ClN_3O$ and its mass spectrum displayed a parent ion distribution of m/e 263/261. The i.r. spectrum of the product confirmed the presence of an amide group and its ^1H n.m.r. spectrum was in accord with the chloroacetamide structure (445) in particular exhibiting a two-proton singlet at δ2.98 attributable to the chloromethyl moiety. Subsequently the chloro-compound (445) was subjected to the normal phosphoryl



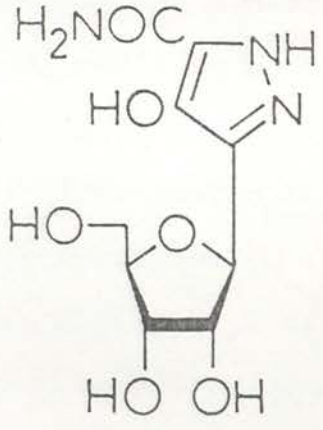
(447)



(448)



(449)



(450)

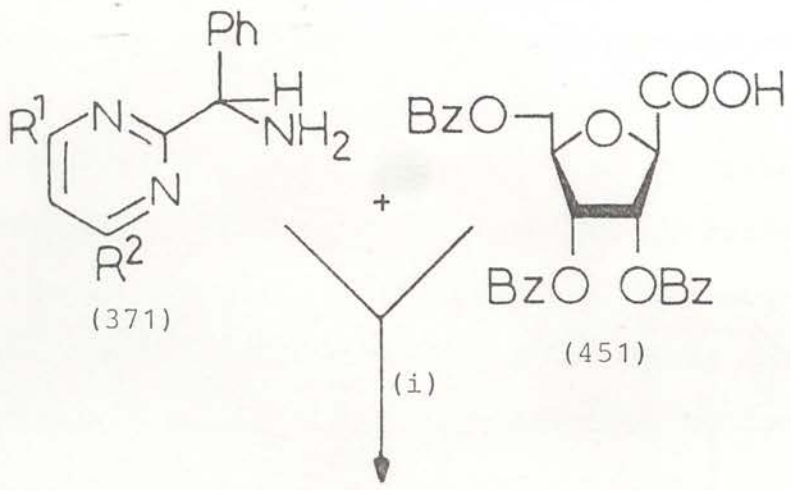
Scheme 113

chloride cyclisation conditions however, as in the analogous pyrazine case, none of the expected product (446) was obtained. Instead a complex mixture was produced and therefore investigations in this area were not continued.

A further target it was thought might be amenable via the aforementioned strategy was the introduction of a ribofuranosyl moiety at the 6-position of the imidazo[1,5-a]pyrimidine nucleus to thereby provide access to a series of novel C-nucleosides. The following section describes the synthesis of such compounds.

3.5 Imidazo[1,5-a]pyrimidine 6-C-Nucleosides

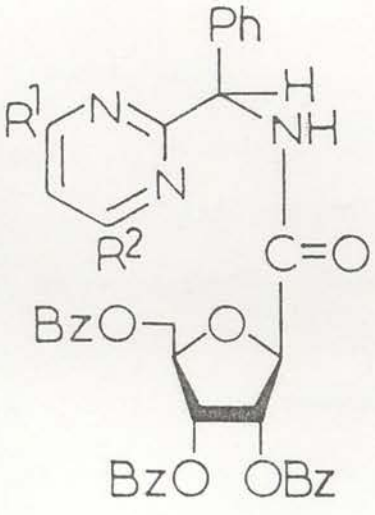
The C-nucleosides[159,160] are a group of compounds which possess a carbon-carbon linkage between the carbohydrate and heterocyclic components in contrast to N-nucleosides in which the two moieties are attached via a carbon-nitrogen bond and this unique structural feature makes these compounds comparatively more stable towards acid and enzymatic cleavage than N-nucleosides. Perhaps the best known of the naturally occurring C-nucleosides (Scheme 113) is formycin A (447) which is a structural analogue of adenosine (448) and which exhibits antibacterial and antiviral properties. Showdomycin (449) and pyrazomycin (450) are further examples of naturally-occurring C-nucleosides[161-163] which display interesting biological properties. Thus it is the biological activity shown by most of the naturally occurring C-nucleosides which has stimulated the intense effort towards the synthesis of analogues of these compounds and therefore it appeared of interest to attempt the preparation of a C-nucleoside derivative of the imidazo[1,5-a]-



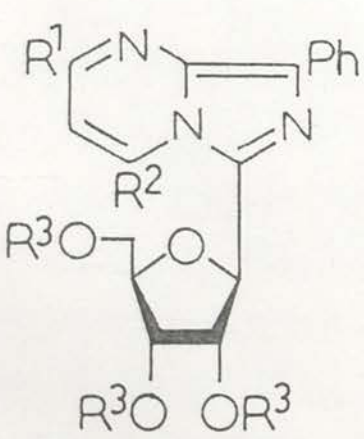
(371)

(451)

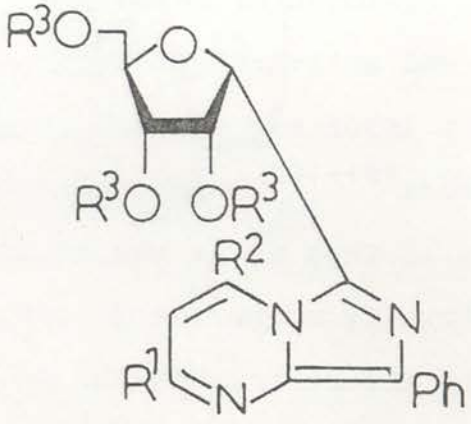
	R^1	R^2
a;	Me	Me
b;	Me	H
c;	H	H
d;	H	Me



(452)



(453)



(454)

R^3 = H or Bz (benzoyl)

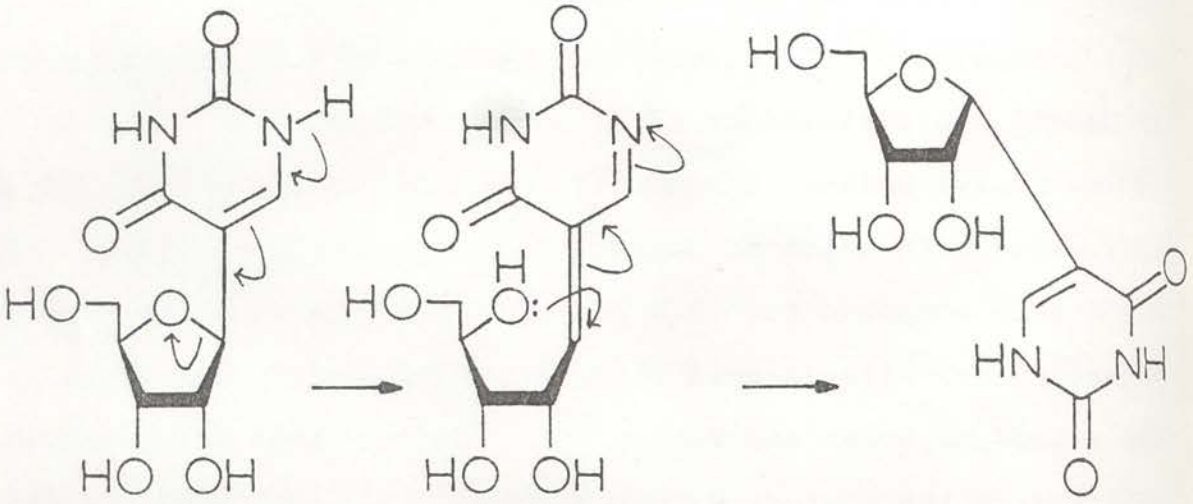
(i) DCC

(ii) $POCl_3$

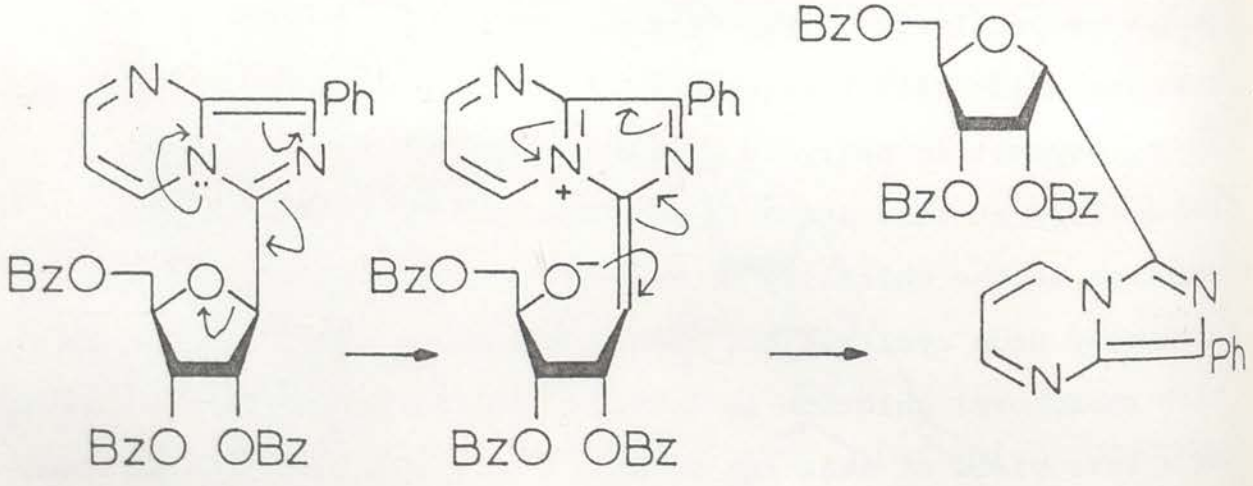
Scheme 114

pyrimidine ring system. Moreover only a few C-nucleosides containing a bridgehead nitrogen atom in the heterocyclic moiety have been reported in the literature.[164-170]

Extension of the already proven synthesis of 6-substituted imidazo[1,5-a]pyrimidines to allow incorporation of a 6-β-D-ribofuranosyl moiety (Scheme 114) required an appropriate sugar derivative with which to acylate the aminoalkylpyrimidines (371). A suitable compound for this purpose is 2,5-anhydro-3,4,6-tri-O-benzoyl-β-D-allonic acid (451) which is readily available by the method of Bobek and Farkas.[171] The reaction of the amine (371c) with the protected carbohydrate acid (451) with the aid of dicyclohexylcarbodi-imide (DCC) as a dehydrating agent afforded the amide (452c) in a good yield as a colourless foam. Elemental analysis of the foam was in accord with the molecular formula $C_{38}H_{31}N_3O_8$ and its mass spectrum showed the anticipated parent ion at m/e 657. The i.r. spectrum of the product contained carbonyl absorptions at 1680 cm^{-1} and 1720 cm^{-1} attributable to the amide group and the ester function of the protecting benzoyl groups respectively. Furthermore its ^1H n.m.r. spectrum showed that the amide (452c) existed as a 1:1 diasterioisomeric mixture at the asymmetric benzylic C-atom. However the production of two isomers at this stage is not detrimental to the synthetic sequence as the chirality at the benzylic C-atom is subsequently destroyed upon cyclisation. When the amide (452c) was heated with phosphoryl chloride in 1,2-dichloroethane (Scheme 114) as well as a fair yield of starting material, a yellow foam was obtained which gave combustion analysis data consistent with the anticipated molecular formula $C_{38}H_{29}N_3O_7$ in agreement with the mass spectrum parent ion (m/e 639). Although the yellow foam



(455) (456) (457)



(458) (459) (460)

Bz = Benzoyl

Scheme 115

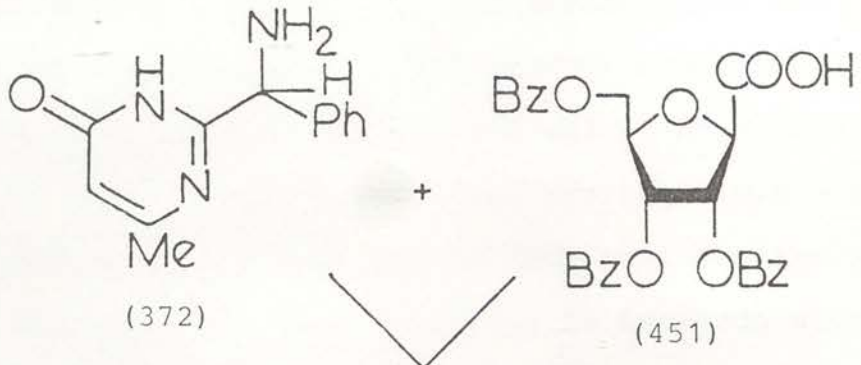
appeared to be t.l.c. pure its ^{1}H n.m.r. spectrum suggested that it was in fact a mixture of the desired β-anomer (453c; R^3=Bz) and an isomer in a ratio of about 70:30. On the basis that the minor isomer exhibits a 1' proton resonance as a doublet at δ6.14, in comparison to the β-anomer whose 1' proton resonates as a doublet at δ5.79, the by-product is tentatively assigned the α-anomer structure (454c; R^3=Bz). This is in accord with the known[172] behaviour of nucleosides in which the α-1' proton generally resonates about 0.5 p.p.m. downfield of the respective β-1' proton. The formation of an α-anomer at this point was unexpected however such a β to α isomerisation finds precedent (Scheme 115) in the acid or base-catalysed equilibration of the naturally occurring β-pseudouridine (455) with its α-anomer (457) reported to proceed via the carbohydrate ring-opened species (456). In the 6-ribofuranosylimidazo-[1,5-a]pyrimidine series participation of the bridgehead nitrogen lone pair may account for such β-isomer to α-isomer anomerisation via intermediate betaine (459). The protected nucleoside α- and β-anomers (433; R^2=Bz) and (454; R^3=Bz) could not be separated and therefore the isomeric mixture was subjected to deprotection (Scheme 114) in methanolic ammonia and subsequent fractional crystallization afforded the major product as a yellow solid in fair yield. The i.r. spectrum of the solid showed the sugar hydroxy-groups absorbing at 3400-3200 cm^{-1} and elemental analysis provided the molecular formula $C_{17}H_{17}N_3O_4$ in agreement with the parent ion contained in the mass spectrum at m/e 327 thereby allowing the substance to be assigned the desired 8-phenyl-6-β-D-ribofuranosylimidazo[1,5-a]pyrimidine structure (453; R=H). Confirmation of this assignment was

obtained from the ^{1}H n.m.r. spectrum of the compound which, as well as containing a phenyl group and a trio of double-doublets for the ABX system of H-2, H-3 and H-4 of the bicyclic imidazo[1,5-a]pyrimidine component, also exhibited a one-proton doublet at δ5.19 (assigned to H-1') coupled to a one-proton triplet at δ4.58 in turn coupled to another one-proton triplet at δ4.15 (for H-2' and H-3' respectively). H-4' appeared as a one-proton quartet at δ3.97 coupled to a two-proton doublet of quartets at δ3.62 attributable to the C-5' methylene protons in accord with the deprotected ribofuranosyl moiety. The β-configuration at the anomeric C-atom is assigned on the basis that the configuration of the sugar precursor [i.e. Scheme 114; (451)] is known[171] to be wholly β. Furthermore when the crystallization mother liquors were evaporated ^{1}H n.m.r. spectroscopy of the resulting gum showed it to be a mixture of the product (453; R=H) and another substance tentatively formulated as the α-nucleoside (454; R=H) due to its exhibition of an anomeric proton resonance about 0.3 p.p.m. downfield of the major product (453; R=H).

In an analogous fashion to that described above (Scheme 114) the amines (371a) and (371b) were reacted with the ribofuranosyl precursor (451) to provide excellent yields of the amides (452a) and (452b) respectively both of which exhibited analytical and spectroscopic properties entirely consistent with their assigned structures (although again each amide was obtained as a 1:1 diastereoisomeric mixture at the benzylic C-atom). On treatment of the amide (452a) with phosphoryl chloride a four component mixture resulted, the major component (53%) of which was identified as unreacted starting material. A yellow foam isolated in 23%

yield was identified as the protected β-nucleoside (453a; R=Bz) by its ^{1}H n.m.r. spectrum. In particular the appearance of the two pyrimidine methyl groups as distinct resonances at δ2.50 and δ2.80 indicated that cyclisation had occurred and the carbohydrate proton resonances, stretched out between δ4.40 and δ7.00, confirmed the presence of the protected nucleoside. It is interesting to note that the 2'-proton of the protected nucleoside (453a) exhibits a pronounced downfield shift suggesting the close proximity of this proton to the 7-nitrogen atom. This can be explained by the steric strain between the 4-methyl substituent and the ribofuranosyl ring causing severely restricted rotation of the latter thereby locking the carbohydrate moiety into a position in which this through-space deshielding effect can occur. Construction of a space-filling model of this compound confirms that just such a locked conformation can occur. Again the β-configuration was assigned to this compound on the basis that a minor product (15%) isolated in the same reaction was identified as the corresponding α-anomer (454a; R=H), its anomeric proton resonating 0.34 p.p.m. downfield to that of the desired β-anomer. Another minor product (8%) obtained in this reaction was shown by its ^{1}H n.m.r. spectrum to contain no sugar moiety. Subsequently the compound was identified as 2,4-dimethyl-6,8-diphenylimidazo[1,5-a]pyrimidine [i.e. Scheme 100; (404a)] whose origin is not immediately apparent. However a possible explanation for the formation of the compound (404a) is an amide exchange of the allonic acid group for some benzoic acid (produced by partial hydrolysis of the sugar protecting groups) followed by subsequent cyclisation. Because of the low yield of the desired product (453a; R=Bz) in this reaction

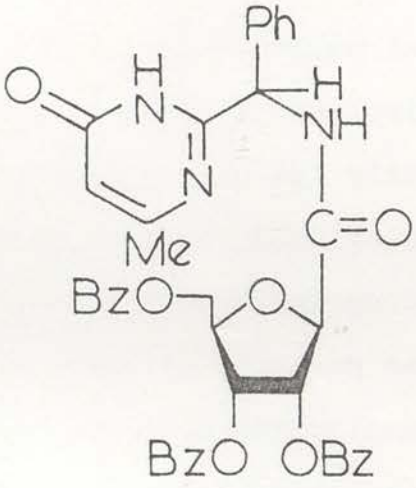
the deprotection of (453a; R=Bz) to (453a; R=H) was not performed. The amide (452b) was also cyclised in phosphoryl chloride-dichloroethane (Scheme 114) to provide a complex mixture. Separation of the mixture gave initially an orange gum whose ^{1}H n.m.r. spectrum again showed the absence of any sugar moiety and was identical to the ^{1}H n.m.r. spectrum of the product mixture obtained on cyclisation of the benzamide [i.e. Scheme 100; (410b)]. This mixture has already been identified as a 2:1 mixture of the isomeric 2- and 4-methyl-6,8-diphenyl-imidazo[1,5-a]pyrimidines (404b) and (404d) and is presumably formed by an identical mechanism to that detailed above. However the major component isolated in this reaction was a yellow foam which analysed correctly for the molecular formula $C_{39}H_{31}N_3O_7$ and whose mass spectrum displayed the appropriate parent ion at m/e 653. Although the foam appeared to be t.l.c. pure its ^{1}H n.m.r. spectrum suggested the presence of two isomers. Particularly evident within the complicated spectrum were two doublets at δ5.77 and δ5.86 attributable to the 1'-protons of different isomers and the absence of any anomeric proton resonances above δ6.00 further suggests that no α-anomer has been isolated in this case. It must therefore be concluded that the foam is a mixture of the 2-methyl and 4-methyl isomers (453b; R^3=Bz) and (453d; R^3=Bz) with the former dominating in the ratio 70:30. Unchanged starting material was also isolated from the mixture in moderate yield (21%). The isomeric mixture of protected nucleosides (453b and d; R^3=Bz) was deprotected using methanolic ammonia and subsequent fractional crystallization of the residue gave the pure product as a yellow solid whose analytical and spectroscopic properties were entirely consistent with the



(372)

(451)

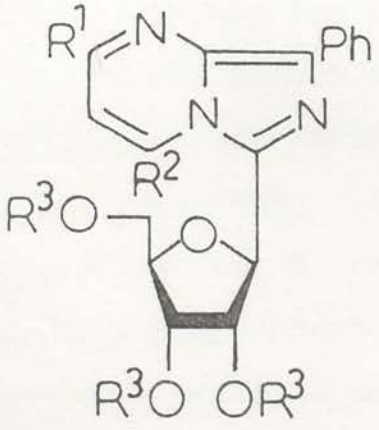
(i)



(461)

	R^1	R^2	R^3
a;	Me	Cl	Bz
b;	Cl	Me	Bz
c;	Me	Cl	H
d;	Cl	Me	H

(ii)



(462)

(i) DCC

(ii) $POCl_3$

R^3 = H or Bz (benzoyl)

Scheme 116

2-methyl-8-phenyl-6-β-D-ribofuranosylimidazo[1,5-a]pyrimidine structure (453b; R^2=H). In particular the ^{1}H n.m.r. of the nucleoside displayed the two pyrimidine protons as a doublet of doublets neither of which was coupled to the ring methyl group therefore establishing its position at C-2. The successful preparation of the imidazo[1,5-a]pyrimidine nucleus ribosylated in the 6-position prompted an attempt (Scheme 116) to extend the synthetic sequence to the aminobenzylpyrimidinone (372). Thus the amine (372) was reacted with the sugar-acid (451) in the presence of dicyclohexylcarbodi-imide to afford the coupled amide (461) in good yield as a colourless foam. The i.r. spectrum of the foam contained a carbonyl absorption at 1670 cm^{-1} for the amide group as well as a peak at 1730 cm^{-1} attributable to the ester function of the benzoyl protecting groups. Elemental analysis agreed with the molecular formula $C_{39}H_{33}N_3O_9$ and the mass spectrum displayed a parent ion at m/e 687. Additionally the ^{1}H n.m.r. spectrum of the product while showing that the amide existed as a 1:1 diastereoisomeric mixture, was consistent with the structure (461). Consequently the amide (461) was cyclised (Scheme 116) to produce a good yield of yellow foam which analysed correctly for the molecular formula $C_{39}H_{30}ClN_3O_7$ in agreement with the parent ion distribution in the mass spectrum at m/e 688/686 indicative of a monochloro-containing compound. However the ^{1}H n.m.r. spectrum of the product showed that the foam was a complex mixture of isomers [i.e. probably (462a) and (462b) and their respective α-anomers]. Separation of this complex mixture was not possible and therefore studies in this area were concluded.

3.6 Experimental

The Attempted Reaction of 2-(α-Chlorobenzyl)-4,6-dimethylpyrimidine (346a) with Ammonia

The chloro-compound (346a), (0.698 g, 0.003 mol) was added to liquid ammonia (25.0 ml) contained in a steel autoclave at -78° (solid CO_2-acetone bath). The autoclave was sealed and allowed to come up to room temperature over 24 h. The autoclave was re-cooled to -78° (solid CO_2-acetone bath) then unsealed and the ammonia allowed to evaporate in a fumehood overnight. The resulting solid residue was treated with water (10.0 ml) and the insoluble solid was collected to give unchanged starting-material (346a) (0.59 g; 85%) identical (m.p. and i.r. spectrum) to an authentic sample.

Work-up of the basic aqueous mother liquor gave no further material.

The Attempted Reaction of 2-(α-Chlorobenzyl)-4,6-dimethylpyrimidine (346a) with Methylamine

The chloro-compound (346a), (0.47 g, 0.002 mol) was stirred at room temperature with a 33% w/v solution of methylamine in ethanol (20.0 ml) for 17 h. Evaporation of the mixture gave a gum (0.68 g) which was treated with ether to afford unchanged starting-material (346a) (0.25 g; 54%), identical (m.p. and i.r. spectrum) to an authentic sample.

Evaporation of the ethereal mother liquor gave a gum (0.26 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

The Attempted Reaction of 2-(α-Chlorobenzyl)-4,6-dimethylpyrimidine (346a) with Benzylamine

The chloro-compound (346a), (0.47 g, 0.002 mol) was stirred at room temperature with benzylamine (0.43 g, 0.004 mol) in absolute ethanol (10.0 ml) for 22 h. Evaporation of the resulting solution gave an orange residue which was treated with water (10.0 ml) and extracted with methylene chloride to give an orange gum (0.54 g). Trituration with b.p. 40-60° light petroleum gave unchanged starting-material (346a) (0.24 g; 52%) identical (m.p. and i.r. spectrum) to an authentic sample.

Evaporation of the light petroleum mother liquor gave only a small amount of a dark gum.

The Attempted Reaction of 2-(α-Chlorobenzyl 6-methylpyrimidin-4(3H)-one (350) with Ammonia

The chloro-compound (350), (0.47 g, 0.002 mol) was added to liquid ammonia (25.0 ml) contained in a steel autoclave at -78° (solid CO_2-acetone bath). The autoclave was sealed and allowed to come to room temperature over 72 h. The autoclave was re-cooled to -78° (solid CO_2-acetone bath) then unsealed and the ammonia allowed to evaporate in a fumehood overnight. Treatment of the resulting gummy residue with water (10.0 ml) gave a basic aqueous solution which was neutralised with 2M aqueous sulphuric acid and solid sodium acetate. Filtration afforded a small amount of fawn solid which was combined with further material obtained by extraction of the aqueous filtrate with methylene chloride to give 2-(α-hydroxybenzyl)-6-methylpyrimidin-4(3H)-one (352) (0.078 g; 19%) as cream crystals, m.p. 187-189° (from toluene-ethanol), ν_{max} 3500-3250br (OH) and

1650 (CO) cm^{-1}.

Found: M^+, 216.09030.

$C_{12}H_{12}N_2O_2$ requires: M, 216.08987.

The aqueous mother liquor was evaporated and the inorganic cake extracted with boiling ethyl acetate to yield a further crop of the alcohol (352) (0.078 g; total 38%) identical (m.p. and i.r. spectrum) to a sample obtained before.

2-(α-N-Methylaminobenzyl)-6-methylpyrimidin-4(3H)-one (353a)

The chloro-compound (350), (1.17 g, 0.005 mol) was stirred at room temperature with a 33% w/v of methylamine in ethanol (50.0 ml) for 17 h. The resulting solution was evaporated and the residue was treated with water (5.0 ml) to give a solid which was combined with a second crop obtained by extracting the aqueous mother liquor to afford 2-(α-N-methylaminobenzyl)-6-methylpyrimidin-4(3H)-one (353a) (1.04 g; 91%) which formed cream crystals, m.p. 175-177° (from toluene), ν_{max} 3200sh and 2600sh (NH) and 1670 (CO) cm^{-1}, $\delta(CDCl_3)$ 7.30-7.10 (5H, m, ArH), 6.00 (1H, s, H-5), 4.45 (1H, s, benzylic CH), 2.30 (3H, s, CH_3) and 2.10 (3H, s, CH_3).

Found: C, 67.6; H, 6.4; N, 17.8%; M^+, 229.

$C_{13}H_{15}N_3O$ requires: C, 68.1; H, 6.6; N, 18.3%; M, 229.

2-(α-N-Benzylaminobenzyl)-6-methylpyrimidin-4(3H)-one (353b)

A solution of the chloro-compound (350), (0.47 g, 0.002 mol) in absolute ethanol (10.0 ml) was mixed with benzylamine (0.43 g, 0.004 mol) and the mixture was stirred at room temperature for 17 h. Evaporation of the mixture gave a crimson gum

which, when treated with ether, gave an insoluble yellow solid (0.20 g) shown (m.s. and elemental analysis) to be benzylamine hydrochloride. The ethereal filtrate was evaporated and the residue was treated with water (10.0 ml) and extracted with ethyl acetate to give a gum (0.32 g) which was triturated with ether to yield unchanged starting-material (350) (0.13 g; 29%) identical (m.p. and i.r. spectrum) to an authentic sample.

Evaporation of the ethereal mother liquor gave a gummy mixture which when treated with picric acid in ethanol produced the picrate salt of 2-(α-N-benzylaminobenzyl)-6-methylpyrimidin-4(3H)-one (353b) (0.11 g; 10%) as yellow crystals, m.p. 196-197° (from ethanol-water), ν_{max} 3200sh (NH) and 1675 (CO) cm^{-1}.

Found: C, 56.4; H, 4.3; N, 15.7%; M^+, 303.

$C_{25}H_{22}N_6O_8$ requires: C, 56.2; H, 4.2; N, 15.4%; M, 534.

The Attempted Reaction of 2-(α-Chlorobenzyl)-6-methylpyrimidin-4(3H)-one (350) with Hexamethylenetetramine

Solutions of the chloro-compound (350), (0.94 g, 0.004 mol) in methylene chloride (15.0 ml) and hexamethylenetetramine (0.56 g, 0.004 mol) in methylene chloride (15.0 ml) were mixed and heated under reflux for 30 min. The mixture was evaporated, treated with water (10.0 ml) and filtered to give unchanged starting-material (350) (0.88 g; 94%) identical (m.p. and i.r. spectrum) to an authentic sample.

The Reaction of 2-(α-Chlorobenzyl)-6-methylpyrimidin-4(3H)-one (350) with Sodium Cyanide

Solutions of the chloro-compound (350), (0.47 g, 0.002 mol)

in ethanol (7.0 ml) and sodium cyanide (0.20 g, 0.004 mol) in water (3 ml) were mixed and the mixture was heated under reflux for 1 h during which the initially yellow solution turned red-brown. The mixture was evaporated, treated with water (5.0 ml) and neutralised with 2M aqueous hydrochloric acid and solid sodium acetate. Extraction with methylene chloride left a colourless solid insoluble which was collected to give the alcohol (352), (0.04 g; 8%) identical (m.p. and i.r. spectrum) to a sample obtained previously.

Evaporation of the methylene chloride phase gave a red gum (0.34 g) which was triturated with light petroleum to yield the ethoxy-compound (355), (0.28 g; 57%) identical (m.p. and i.r. spectrum) to a sample obtained before.

4,6-Dimethyl-2-(α-thiocyanatobenzyl)pyrimidine (359)

Solutions of the chloro-compound (346a), (0.47 g, 0.002 mol) in ethanol (7.0 ml) and sodium thiocyanate (0.32 g, 0.004 mol) in water (3.0 ml) were mixed and the mixture was heated under reflux for 1 h. The mixture was evaporated, treated with water (5.0 ml) and filtered to give an orange solid (0.49 g), ν_{max} 2160 and 2040 cm^{-1}, whose t.l.c. in ethyl acetate over silica showed it to be a multicomponent mixture. Preparative t.l.c. of the solid in ethyl acetate over silica followed by crystallisation afforded 4,6-dimethyl-2-(α-thiocyanatobenzyl)pyrimidine (359) (0.37 g; 72%) as irregular lemon crystals, m.p. 103-104° (from light petroleum-toluene), ν_{max} 2160 (SCN) cm^{-1}, $\delta(CDCl_3)$ 7.50-7.20 (5H, m, ArH), 6.92 (1H, s, H-5), 5.76 (1H, s, benzylic CH) and 2.44 (6H, s, CH_3).

Found: M^+, 255.08350.

$C_{14}H_{13}N_3S$ requires: M, 255.08301.

The reaction of 2-(α-Chlorobenzyl)-4,6-dimethylpyrimidine (346a) with Disodium Cyanamide

Solutions of the chloro-compound (346a), (0.47 g, 0.002 mol) in ethanol (14.0 ml) and disodium cyanamide (0.34 g, 0.004 mol) in water (6.0 ml) were mixed and the mixture was heated under reflux for 30 min when a second portion of disodium cyanamide (0.34 g, 0.004 mol) was added and heating was continued for a further 30 min. The mixture was evaporated, treated with water (10.0 ml) and extracted with methylene chloride to give an orange gum (0.41 g) which was triturated with ether to give a small amount of the urea (364) (0.03 g), m/e 256. Evaporation of the ether mother liquor gave a red oil (0.36 g) whose t.l.c. in ether over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

Work-up of the basic aqueous mother liquor gave no further material.

2-Benzoyl-6-methylpyrimidin-4(3H)-one (366)

Solutions of the chloro-compound (350), (11.70 g, 0.05 mol) in ethanol (90.0 ml) and sodium azide (6.50 g, 0.1 mol) in water (38.0 ml) were mixed and the mixture was heated under reflux for 1.5 h. The mixture was evaporated, treated with water (30.0 ml) and filtered to yield a pale yellow solid which was combined with a second crop obtained by neutralizing the basic aqueous mother liquor with glacial acetic acid to give 2-benzoyl-6-methylpyrimidin-4(3H)-one (366) (9.94 g; 93%) which formed

yellow needles, m.p. 152-154° (from ethyl acetate), ν_{max} 1675 (CO) cm^{-1}, $\delta(CDCl_3)$ 8.40-8.30 (2H, m, ArH), 7.70-7.30 (3H, m, ArH), 6.50 (1H, s, H-5) and 2.38 (3H, s, CH_3).

Found: C, 67.2; H, 4.6; N, 12.9%; M^+, 214.

$C_{12}H_{10}N_2O_2$ requires: C, 67.3; H, 4.7; N, 13.1%; M, 214.

Changing the reaction solvent from ethanol-water (70:30) to dioxane-water (70:30) also produced the ketone (366) as the only product albeit in lower yield (79%).

2-(α-Azidobenzyl)-6-methylpyrimidin-4(3H)-one (365)

Solutions of the chloro-compound (350), (4.7 g, 0.02 mol) in ethanol (140 ml) and sodium azide (5.2 g, 0.08 mol) in water (60.0 ml) were mixed and stirred at room temperature for 24 h. The mixture was concentrated at room temperature to remove the ethanol and filtered to afford 2-(α-azidobenzyl)-6-methylpyrimidin-4(3H)-one (365), (4.4 g; 93%) as colourless needles, m.p. 162-164° (from ethyl acetate), ν_{max} 3500-3300 (NH), 2120 (N_3) and 1660 (CO) cm^{-1} $\delta(CDCl_3)$ 13.00-10.00 (1H, bs, NH), 7.68-7.30 (5H, m, ArH), 6.27 (1H, s, H-5), 5.57 (1H, s, benzylic CH) and 2.45 (3H, s, CH_3).

Found: M^+, 241.09721.

$C_{12}H_{11}N_5O$ requires: M, 241.09635.

The Preparation of 2-(α-Azidobenzyl)pyrimidines

Solutions of the chloro-compound (0.05 mol) in ethanol (105 ml) and sodium azide (6.5 g, 0.05 mol) in water (45.0 ml) were mixed, the mixture was heated under reflux for 1.5 h and worked up as described for the individual reactions below.

(i) The reaction mixture from the chloro-compound (346c) (10.2 g) was concentrated to remove the ethanol and the oily mixture so produced was extracted with methylene chloride to give an orange oil (9.5 g). This was purified by flash chromatography in methylene chloride over silica to afford 2-(α-azidobenzyl)pyrimidine (367c), (9.8 g; 93%) as a colourless oil, ν_{max} 2100 (N_3) cm^{-1}, δ($CDCl_3$) 8.70 (2H, d, J5Hz, H-4 and H-6), 7.60-7.30 (5H, m, ArH), 7.18 (1H, t, J5Hz, H-5) and 5.73 (1H, s, benzylic CH).

Found: M^+, 211.08683 .

$C_{11}H_9N_5$ requires: M, 211.08579 .

(ii) The reaction mixture from the chloro-compound (346b) (10.9 g) was concentrated to remove the ethanol and extracted with methylene chloride to give a colourless oil. The oil crystallised on scratching to afford 2-(α-azidobenzyl)-4-methylpyrimidine (367b), (10.5 g, 94%) which formed colourless needles, m.p. 63-68° (from light petroleum), ν_{max} 2100 (N_3) cm^{-1}, δ($CDCl_3$) 8.60 (1H, d, J5Hz, H-6), 7.70-7.20 (5H, m, ArH), 7.05 (1H, d, J5Hz, H-5), 5.70 (1H, s, benzylic CH) and 2.50 (3H, s, CH_3).

Found: C, 63.9; H, 4.9; N, 30.9%; M^+, 225.

$C_{12}H_{11}N_5$ requires: C, 64.0; H, 4.9; N, 31.1%; M, 225.

(iii) The reaction mixture from the chloro-compound (346a) (11.6 g) was concentrated to remove the ethanol and filtered to afford 2-(α-azidobenzyl)-4,6-dimethylpyrimidine (367a), (12.0 g; quant.) which formed fawn prisms, m.p. 89-90° (from b.p. 40-60° light petroleum-ethanol), ν_{max} 2100 (N_3) cm^{-1}, δ($CDCl_3$) 7.60-7.20 (5H, m, ArH), 6.89 (1H, s, H-5), 5.64 (1H,

s, benzylic CH) and 2.44 (6H, s, CH_3).

Found: C, 64.7; H, 5.5; N, 29.2%; M^+, 239.

$C_{13}H_{13}N_5$ requires: C, 65.2; H, 5.5; N, 29.3%; M, 239.

2-Benzoyl-4,6-dimethylpyrimidine (370a)

(i) The azide (367a), (0.24 g, 0.001 mol) was dissolved in ethanol (5.0 ml), treated with 2M aqueous hydrochloric acid (2.5 ml) and the solution was heated under reflux for 5 h. Evaporation of the mixture produced an orange gum (0.373 g) which was treated with water (5.0 ml) and extracted with methylene chloride to give a brown oil. On standing the oil crystallised to afford 2-benzoyl-4,6-dimethylpyrimidine (370a), (0.16 g, 74%) as cream coloured plates, m.p. 85-86° (lit.[148], m.p. 85-86°) (from light petroleum), ν_{max} 1680 (CO) cm^{-1}, $\delta(CDCl_3)$ 8.10-7.95 (2H, m, ArH), 7.60-7.20 (3H, m. ArH), 7.16 (1H, s. H-5) and 2.58 (6H, s, CH_3).

Found: C, 74.2; H, 5.8; N, 13.5%; M^+, 212.

$C_{13}H_{12}N_2O$ requires: C, 73.6; H, 5.7; N, 13.2%; M, 212.

(ii) A solution of the azide (367a), (0.96 g, 0.004 mol) in glacial acetic acid (10.0 ml) was heated under reflux for 1 h. Evaporation and co-evaporation with toluene gave a brown gum which was treated with water (5.0 ml) and extracted with methylene chloride to produce a brown oil (0.82 g). The oil was triturated with b.p. 40-60° light petroleum-ether to afford the ketone (370a), (0.37 g; 44%) which was identical (m.p. and i.r. spectrum) to a sample prepared in (i) before.

The trituration mother liquor, when evaporated, gave a brown oil (0.45 g) which was shown by t.l.c. in ether over silica to be a multicomponent mixture containing the ketone (370a)

as a major component. The oil was not further investigated.

The Attempted Reduction of 2-(α-Azidobenzyl)-4,6-dimethylpyrimidine (367a)

(i) The azide (367a), (0.96 g, 0.002 mol) was dissolved in 70% (v/v) aqueous ethanol (20.0 ml), treated with sodium dithionite (0.96 g) and the mixture was heated under reflux for 1 h. A second portion of sodium dithionite was then added and heating was continued for a further 1 h. Hot-filtration removed insoluble sodium dithionite and the filtrate was evaporated, treated with water (5.0 ml) and filtered to give the unchanged starting-material (367a) (0.67 g; 70%) identical (m.p. and i.r. spectrum) to an authentic sample.

The aqueous mother liquor was evaporated and the inorganic cake was extracted with boiling ethyl acetate to give a pink gum (0.1 g) whose t.l.c. in methylene chloride over silica showed it to be a three component mixture containing starting material. The gum was not further investigated.

Repetition of the reaction using four weight equivalents of sodium dithionite each added 30 min after the initial addition over a period of 2 h resulted in a good recovery (82%) of unchanged starting material.

(ii) A solution of the azide (367a), (0.48 g, 0.002 mol) in 70% (v/v) aqueous ethanol (20.0 ml) was cooled to 0°C (ice-salt bath), saturated with sulphur dioxide, sealed tightly and left at room temperature for 17 h. Evaporation of the mixture gave a brown oil which was treated with water (5.0 ml) and extracted with methylene chloride to give unchanged starting-material (367a) (0.36 g; 76%) identical (m.p. and i.r. spectrum)

to an authentic sample. Work up of the aqueous mother liquor gave no further material.

The Preparation of 2-(α-Aminobenzyl)pyrimidines

A solution of the azide (0.02 mol) in absolute ethanol (150 ml) was hydrogenated over 10% palladium-on-charcoal (0.1 weight equivalents) at 4 atm. for 5 h and worked up as described for the individual reactions below.

(i) The reaction mixture from the azide (367c) (4.2 g) was filtered through celite and evaporated to afford 2-(α-aminobenzyl)pyrimidine (371c), (3.3 g; 88%) which formed colourless crystals, m.p. 58-60° (from light petroleum-toluene), ν_{max} 3380 and 3310 (NH) cm^{-1}, $\delta(CDCl_3)$ 8.68 (2H, d, J5Hz, H-4 and H-6), 7.50-7.20 (5H, m, ArH), 7.09 (1H, t, J5Hz, H-5), 5.30 (1H, s, benzylic CH) and 2.35 (2H, bs, NH_2).

Found: C, 71.3; H, 6.0; N, 22.5%; M^+, 185.
$C_{11}H_{11}N_3$ requires: C, 71.3; H, 6.0; N, 22.7%; M, 185.

(ii) The reaction mixture from the azide (367b) (4.5 g) was filtered through celite and evaporated to afford 2-(α-aminobenzyl)-4-methylpyrimidine (371b), (4.1 g; 100%) which formed fawn needles, m.p. 79-81° (from light petroleum), ν_{max} 3380 and 3300 (NH) cm^{-1} $\delta(CDCl_3)$ 8.55 (1H, d, J5Hz, H-6), 7.60-7.30 (5H, m, ArH), 6.97 (1H, d, J5Hz, H-5), 5.30 (1H, s, benzylic CH), 2.50 (3H, s, CH_3) and 2.30 (2H, bs, NH_2).

Found: C, 72.3; H, 6.6; N, 21.1%; M^+, 199.
$C_{12}H_{13}N_3$ requires: C, 72.3; H, 6.6; N, 20.9%; M, 199.

(iii) The reaction mixture from the azide (367a) (4.8 g) was filtered through celite and evaporated to afford 2-(α-aminobenzyl)-4,6-dimethylpyrimidine (371a), (4.3 g; quant.)

which formed cream crystals, m.p. 78-80° (from b.p. 80-100° light petroleum), ν_{max} 3380 and 3280 (NH) cm^{-1}, $\delta(CDCl_3)$ 7.50-7.10 (5H, m, ArH), 6.78 (1H, s, H-5), 5.20 (1H, s, benzylic CH) and 2.40 (6H, s, $2CH_3$).

Found: C, 72.6; H, 7.0; N, 19.7%; M^+, 213.

$C_{13}H_{15}N_3$ requires: C, 73.2; H, 7.1; N, 19.7%; M, 213.

2-(α-Aminobenzyl)-6-methylpyrimidin-4(3H)-one and its Mono- and Dihydrochloride Salts

(i) A solution of the azide (365), (0.97 g, 0.004 mol) in absolute ethanol (100 ml) was hydrogenated over 10% palladium-on-charcoal (0.097 g) at 4 atm. for 5 h. The mixture was filtered through celite and the filtrate was treated with aqueous 10% (v/v) hydrochloric acid in ethanol (17.5 ml, 0.02 mol) and evaporated to give a fawn semi-solid. Trituration with hot ethyl acetate-ethanol gave 2-(α-aminobenzyl)-6-methyl-pyrimidin-4(3H)-one (372) dihydrochloride, which was combined with a second crop obtained by chilling the filtrate (total 0.63 g; 54%) and crystallised to give colourless crystals, m.p. 249-255° (from ethanol-water), ν_{max} 3500-3300 (NH), 2700-2500br (hydrochloride salt) and 1660 (CO) cm^{-1}, $\delta[(CD_3)_2SO]$ 11.00-9.00 (2H, bs, 2NH), 7.65-7.55 (2H, m, ArH), 7.55-7.40 (3H, m, ArH), 6.26 (1H, s, H-5), 5.42 (1H, s, benzylic CH) and 2.32 (3H, s, CH_3).

Found: C, 50.2; H, 4.9; N, 13.9%; M^+,215(M-2HCl)

$C_{12}H_{15}Cl_2N_3O$ requires: C, 50.0; H, 5.2; N, 14.6%; M, 288.

Repetition of the reaction gave a colourless product (yield 70%) whose i.r. and ^1H n.m.r. spectra were identical to those obtained before but on crystallisation afforded the amine mono-hydrochloride.

Found: C, 56.6; H, 5.6; N, 16.6%; M^+, 215(M-HCl).

$C_{12}H_{14}ClN_3O$ requires: C, 57.2; H, 5.6; N, 16.7%; M, 251.5.

(ii) A solution of the azide (365), (2.9 g, 0.012 mol) in absolute ethanol (200 ml) was hydrogenated over 10% palladium-on-charcoal (0.29 g) at 4 atm. for 5 h. Filtration through celite and evaporation of the filtrate afforded 2-(α-aminobenzyl)-6-methylpyrimidin-4(3H)-one (372), (2.8 g; 100%) ν_{max} 3570, 3470, 3360 and 3300 (NH) and 1685 and 1660 (CO) cm^{-1}, $\delta(CDCl_3)$ 7.50-7.20 (5H, m, ArH), 6.10 (1H, s, H-5), 5.02 (1H, s, benzylic CH), 5.0-3.4 (3H, bs, 3NH) and 2.22 (3H, s, CH_3).

Found: M^+, 215.10509.

$C_{12}H_{13}N_3O$ requires: M, 215.10586.

The Baeyer-Villiger Oxidation of 2-Benzoyl-6-methylpyrimidin-4(3H)-one (366)

The ketone (366), (1.7 g, 0.008 mol) in glacial acetic acid (30.0 ml) was treated with 30% aqueous hydrogen peroxide (20.0 ml) and the mixture was stirred at 50° (oil bath) for 17 h during which time the yellow colour was completely discharged. The colourless mixture was diluted with water (50.0 ml), neutralised with solid sodium acetate and extracted with methylene chloride to afford benzoic acid (0.60 g, 62%) identical (m.p. and i.r. spectrum) to an authentic sample.

Work-up of the aqueous mother liquor gave no further identifiable material.

The Preparation of 2-(α-Oximinobenzyl)pyrimidines

A solution of the ketone (0.002 mol) in ethanol (10.0 ml) was treated with hydroxylamine hydrochloride (0.004 mol) and anhydrous sodium acetate (0.006 mol). The mixture was heated under reflux for 5 h and worked up as described for the individual reactions below.

(i) The reaction mixture from the ketone (370a) (0.42 g) was evaporated, treated with water (10.0 ml) and filtered to yield 4,6-dimethyl-2-(α-oximinobenzyl)pyrimidine (390), (0.44 g; 97%) which formed colourless rhombic crystals, m.p. 192-194° (from ethanol-dimethylformamide), ν_{max} 3240-3100 (OH) cm^{-1}, δ[$(CD_3)_2SO$] 11.70 (1H, s, oxime OH), 7.38 (5H, s, ArH), 7.23 (1H, s, H-5) and 2.39 (3H, s, CH_3).

Found: C, 68.5; H, 5.9; N, 18.5%; M^+, 227.

$C_{13}H_{13}N_3O$ requires: C, 68.7; H, 5.8; N, 18.5%; M, 227.

(ii) The reaction mixture from the ketone (366) (0.43 g) was evaporated, treated with water (10.0 ml) and filtered to afford 6-methyl-2-(α-oximinobenzyl)pyrimidin-4(3H)-one (376a) as a mixture of the (Z) and (E) isomers, (0.44 g; 96%) which formed colourless needles, m.p. 242° (from toluene-ethanol), ν_{max} 3300 and 3220-3120 (NH) and 1680br (CO) cm^{-1}, δ[$(CD_3)_2SO$] 9.60-9.00 (1H, bs, oxime OH), 7.39 (5H, s, ArH), 6.20 and 6.18 (1H, s, H-5) and 2.21 and 2.11 (3H, s, CH_3).

Found: M^+, 229.08564.

$C_{12}H_{11}N_3O_2$ requires: M, 229.08512.

The ^1H n.m.r. spectrum of the oxime (376a) showed no signal coalescence over the temperature range 20-103°.

The Attempted Reduction of 6-Methyl-2-(α-oximinobenzyl)pyrimidin-4(3H)-one (376a)

(i) A solution of the oxime (376a), (0.46 g, 0.002 mol) in ethanol (30.0 ml) was hydrogenated over 10% palladium-on-charcoal (0.046 g) at atmospheric pressure and room temperature for 6 h. The mixture was filtered through celite and the filtrate was

evaporated to give unreacted starting material (376a) (0.38 g, 83%) identical (m.p. and i.r. spectrum) to an authentic sample.

(ii) A solution of the oxime (376a), (0.40 g, 0.0018 mol) in 70% (v/v) aqueous ethanol (10.0 ml) was treated with sodium dithionite (0.40 g) and the mixture was heated under reflux for 30 min after which time a second portion of sodium dithionite (0.40 g) was added. Heating was continued for a further 30 min and the mixture was hot-filtered to remove the excess of the sodium dithionite. Evaporation of the filtrate and treatment of the residue with water (5.0 ml) gave unchanged starting-material (376a) (0.20 g; 50%) identical (m.p. and i.r. spectrum) to an authentic sample.

The aqueous filtrate was evaporated and the inorganic cake was extracted with boiling ethyl acetate to yield a yellow gum (0.15 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

(iii) A solution of the oxime (376a), (1.15 g, 0.005 mol) in 3M aqueous sodium hydroxide was treated with sodium dithionite (2.05 g, 0.01 mol) and the mixture was stirred at room temperature for 1 h. The mixture was neutralised with concentrated hydrochloric acid and solid sodium acetate and the deposited solid was collected to give unchanged starting-material (1.15 g, 100%) identical (m.p. and i.r. spectrum) to an authentic sample.

(iv) A solution of the oxime (376a), (1.15 g, 0.005 mol) in absolute ethanol (100 ml) was hydrogenated over 10% palladium-on-charcoal (0.12 g) at 4 atm. for 5 h. Filtration through celite and evaporation of the filtrate afforded unchanged starting-material (376a) (0.15 g; 100%) identical m.p. and i.r.

spectrum to an authentic sample.

Repetition of the reaction using a hydrogen pressure of 6 atm. also gave only unchanged starting-material (87%).

(v) In a variation of the conditions described in (iv) before, the oxime (376a), (1.15 g, 0.005 mol) in glacial acetic acid (70.0 ml) was hydrogenated over 10% palladium-on-charcoal at 4 atm. for 5 h. Filtration of the reaction mixture through celite and evaporation of the filtrate gave a brown solid (1.24 g) which was shown by t.l.c. in ethanol over silica to be a two-component mixture containing the starting-material. The ^1H n.m.r. spectrum of the mixture showed that it contained the oxime (376a) as a single geometrical isomer and a second product which showed ^1H n.m.r. absorption at δ4.84 (benzylic CH).

The solid mixture (0.55 g) was treated with 2M aqueous hydrochloric acid (20.0 ml) and stirred at room temperature for 30 min. Filtration afforded the oxime (376a) as a single geometrical isomer (0.16 g) which formed colourless needles, m.p. 239-243° (from toluene-ethanol), ν_{max} 3160 (OH or NH) and 1675 (CO) cm^{-1}, δ[$(CD_3)_2SO$] 12.60-12.00 (1H, bs, oxime OH), 7.40 (5H, s, ArH), 6.20 (1H, s, H-5) and 2.12 (3H, s, CH_3).

Found: C, 62.8; H, 4.7; N, 18.5%; M^+, 229.
$C_{12}H_{11}N_3O_2$ requires: C, 62.9; H, 4.8; N, 18.3%; M, 229.

The acidic aqueous filtrate was neutralised with aqueous 2M sodium hydroxide and glacial acetic acid and extracted with methylene chloride to give an unidentified yellow solid (0.11 g).

(vi) A solution of the oxime (376a), (0.46 g; 0.002 mol) in absolute ethanol (70.0 ml) containing concentrated hydrochloric acid was hydrogenated over 10% palladium-on-charcoal (0.046 g) at 4 atm. for 5 h. The mixture was filtered through celite and

the filtrate was evaporated to give a green gum (0.74 g) which was treated with water (20.0 ml) to give unchanged starting-material (0.25 g; 55%). Evaporation of the aqueous filtrate gave a yellow solid (0.38 g) which could not be characterised.

2-(α-Acetoxyiminobenzyl)-6-methylpyrimidin-4(3H)-one (376b)

(i) The oxime (376a), (0.46 g, 0.002 mol) was treated dropwise with acetic anhydride (0.5 ml) to give a paste which was heated at 100° (hot-water bath) until the solid had completely dissolved (3-4 min). Heating was continued for a further 10 min after which time the solution was allowed to cool slowly to room temperature. Treatment with ether precipitated the solid oxime-acetate (376b), (0.18 g; 32%) which formed colourless prisms, m.p. 178-180° (from light petroleum-toluene), ν_{max} 1780 and 1685 (CO) cm^{-1}, $\delta(CDCl_3)$ 7.43 (5H, s, ArH), 6.31 (1H, s, H-5), 2.21 (3H, s, CH_3) and 2.13 (3H, s, CH_3).

Found: C, 61.7; H, 4.8; N, 15.6%; M^+, 271.

$C_{14}H_{13}N_3O_3$ requires: C, 62.0; H, 4.8; N, 15.5%; M, 271.

Evaporation of the ethereal mother liquor gave a yellow oil which was treated with water (5.0 ml) and extracted with methylene chloride leaving a solid insoluble which was combined with further material obtained by evaporating the methylene chloride extract to give unreacted starting-material (total 0.2 g; 45%) identical (m.p. and i.r. spectrum) to an authentic sample.

(ii) The oxime (376a), (0.46 g, 0.002 mol) was treated dropwise with acetic anhydride (0.5 ml) to give a paste which was treated with concentrated sulphuric acid (4 drops) whereupon the solid dissolved. The mixture was kept at room temperature for 20 min and then treated with ice (2.0 g) to precipitate

unchanged starting-material (376a) which was combined with a second crop obtained by extraction of the aqueous mother liquor with methylene chloride (total 0.33 g; 73%) identical (m.p. and i.r. spectrum) to an authentic sample.

(iii) The oxime (376a), (0.46 g, 0.002 mol) was dissolved in acetic anhydride (1.0 ml), treated with fused sodium acetate (0.18 g, 0.0022 mol) and the mixture was heated under reflux for 2-3 min. After cooling the mixture was treated with water (5.0 ml) and extracted with methylene chloride to give a green gum which was triturated with ether to afford a solid which was combined with a second crop obtained by evaporation of the trituration liquor (total 0.26 g; 48%) identical (i.r. spectrum) to the oxime-acetate (376b) obtained in (i) before.

Neutralisation of the basic aqueous mother liquor with 2M aqueous hydrochloric acid and solid sodium acetate followed by extraction with methylene chloride gave only a small amount of unchanged starting-material (376a) (0.04 g; 8%) identical (m.p. and i.r. spectrum) to an authentic sample.

(iv) The oxime (376a), (0.46 g, 0.002 mol) was dissolved in acetic anhydride (5.0 ml) and heated under reflux for 3 h during which time the solution gradually darkened to a deep brown colour. Evaporation of the mixture gave a black oil (0.50 g) which was triturated with methylene chloride to give low-melting starting-material (376a) (0.10 g; 21%) identical (i.r. spectrum) to an authentic sample. Evaporation of the trituration liquor gave a black gum whose t.l.c. in ether over silica showed it to be a multicomponent mixture which was not further investigated.

(v) A solution of the oxime (376a), (0.46 g, 0.002 mol) in dry 1,2-dimethoxyethane (25.0 ml) was treated with triethyl-

amine (0.25 g, 0.0025 mol) followed by a solution of acetyl chloride (0.17 g, 0.0022 mol) in dry 1,2-dimethoxyethane (1.0 ml) and the mixture was stirred at room temperature for 1 h. The mixture was filtered to remove the precipitated triethylamine hydrochloride and the filtrate was evaporated to give a clear gum (0.61 g) which was triturated with ether to afford the oxime-acetate (376b) (0.19 g; 34%) identical (m.p. and i.r. spectrum) to an authentic sample.

Evaporation of the ethereal mother liquor gave a colourless gum (0.24 g) whose t.l.c. in ethyl acetate over silica showed it to be a three-component mixture containing the oxime starting-material (376a) as a major component. The gum was not further investigated.

The Catalytic Reduction of 2-(α-Acetoxyiminobenzoyl)-6-methyl-pyrimidin-4(3H)-one (376b)

The oxime-acetate (376b), (0.16 g, 0.0006 mol) was hydrogenated in absolute ethanol (30.0 ml) over 10% palladium-on-charcoal (0.016 g) at atmospheric pressure for 6 h. Filtration through celite and evaporation of the filtrate gave a colourless low-melting solid (0.15 g) whose i.r. suggested it was a mixture of the desired amine (372) and the acetamide (377) by comparison with the authentic i.r. spectra.

2-(α-Benzoyloxyiminobenzyl)-6-methylpyrimidin-4(3H)-one (376c)

A solution of the oxime (376a), (0.46 g, 0.002 mol) in dry 1,2-dimethoxyethane (25.0 ml) was stirred and treated with triethylamine (0.25 g, 0.0025 mol) then dropwise with a solution of benzoyl chloride (0.42 g, 0.003 mol) in dry 1,2-dimethoxyethane

(1.0 ml). The mixture was stirred at room temperature for 30 min, filtered to remove triethylamine hydrochloride and evaporated to give a pale yellow gum (0.89 g). This slowly crystallised on standing for 6-7 weeks to give a colourless solid which was collected with ether and combined with a second crop obtained by chilling the ethereal filtrate to give a 1:1-mixture of the (E)- and (Z)-isomers of the oxime-benzoate (376c), (total 0.47 g; 70%) which formed colourless needles, m.p. 186-187° (from toluene), ν_{max} 1760 and 1660 (CO) cm^{-1}, $\delta(CDCl_3)$ 7.90-7.60 (2H, m, ArH), 7.60-7.20 (3H, m, ArH), 6.29 and 6.23 (1H, s, H-5) and 2.30 and 2.16 (3H, s, CH_3),

Found: C, 68.2; H, 4.4; N, 12.8%; M^+, 333.

$C_{19}H_{15}N_3O_3$ requires: C, 68.5; H, 4.5; N, 12.6%; M, 333.

Evaporation of the ethereal filtrate gave a yellow gum (0.22 g) from which no identifiable material could be obtained.

2-(α-p-Toluene sulphonyloxyiminobenzyl)-6-methylpyrimidin-4(3H)-one (376d)

A solution of the oxime (376a), (0.46 g, 0.002 mol) in dry 1,2-dimethoxyethane (25.0 ml) was stirred and treated with triethylamine (0.25 g, 0.0025 mol) followed dropwise by a solution of toluene-p-sulphonyl chloride (0.42 g, 0.0022 mol) in dry dimethoxyethane (1.0 ml). The mixture was stirred at room temperature for 30 min, filtered to remove triethylamine hydrochloride and the filtrate was evaporated to give a yellow gum which was crystallised to yield the oxime-tosylate (376d), (0.42 g, 55%) as colourless needles, m.p. 144-146° (from toluene) ν_{max} 1665 (CO) cm^{-1} $\delta[(CD_3)_2SO]$ 7.82 (2H, d, J8Hz, ArH), 7.52 (2H, d, J8Hz, ArH), 7.46 (5H, m, ArH), 6.48 (1H, s, H-5), 2.43 (3H, s, CH_3) and 2.30 (3H, s, CH_3).

Found: C, 59.9; H, 4.6; N, 11.5%; M^+, 383.

$C_{19}H_{17}N_3O_4S$ requires: C, 59.5; H, 4.5; N, 11.0%; M, 383.

Evaporation of the toluene mother liquor gave a yellow gum (0.28 g) from which no identifiable material could be obtained.

2-(α-Ethoxycarbonyloxyiminobenzyl)-6-methylpyrimidin-4(3H)-one (376e)

A solution of the oxime (376a), (0.46 g, 0.002 mol) in dry acetonitrile (25.0 ml) was stirred and treated with triethylamine (0.51 g, 0.005 mol) followed by ethyl chloroformate (0.24 g, 0.0022 mol) and the mixture was stirred at room temperature for 1 h. The mixture was evaporated, treated with water (10.0 ml) and extracted with methylene chloride to give a yellow gum (0.62 g) which was treated with ether to give a 1:1 mixture of the (Z)- and (E)-isomers of the oxime-carboxylate (376e), (0.18 g; 31%) which formed colourless needles, m.p. 148-150° (from b.p. 80-100° light petroleum-toluene), ν_{max} 1800 and 1670 (CO) cm^{-1}, δ($CDCl_3$) 7.40 (5H, s, ArH), 6.17 (1H, s, H-5), 4.30 (2H, q, J7.0Hz, CH_2), 2.31 and 2.16 (3H, s, CH_3) and 1.30 (3H, t, J7.0Hz, CH_3).

Found: C, 59.9; H, 4.9; N, 14.1%; M^+, 301.

$C_{15}H_{15}N_3O_4$ requires: C, 59.8; H, 5.0; N, 14.0%; M, 301.

Evaporation of the ethereal filtrate gave a brown gum (0.33 g) whose t.l.c. in ethyl acetate over silica showed it to be a three-component mixture containing further product. The gum was not further investigated.

6-Methylpyrimidin-4(3H)-one-2-(N-phenylcarboxamide) (379)

A suspension of the oxime (376a), (0.46 g, 0.002 mol) in polyphosphoric acid (ca.7 ml) was stirred and heated at 120-130° (oil-bath) for 10 min. After cooling the mixture was treated with water (10.0 ml) and the resulting brown solution was neutralised with 2M aqueous sodium hydroxide and glacial acetic acid to afford a solid which was combined with a second crop obtained by extracting the aqueous mother liquor with methylene chloride to give the amide (379), (total 0.32 g; 70%) which formed fawn crystals, m.p. 189-192° (from toluene), ν_{max} 3370-3190 (NH) and 1700-1650br (CO) cm^{-1}, $\delta(CDCl_3)$ 9.51 (1H, s, NH), 8.20-7.00 (2H, m, ArH), 7.50-7.10 (3H, m, ArH), 6.42 (1H, s, H-5) and 2.36 (3H, s, CH_3).

Found: C, 63.0; H, 4.8; N, 18.2%; M^+, 229.
$C_{12}H_{11}N_3O_2$ requires: C, 62.9; H, 4.9; N, 18.3%; M, 229.

The Preparation of 2-Benzoylpyrimidine Hydrazones

A solution of the ketone (0.002 mol) in methanol (50 ml) was treated with hydrazine hydrate (0.002 mol) and the mixture was heated under reflux for 3 h. The reaction mixture was worked up as described for the individual reactions below.

(i) The reaction mixture from the ketone (370a) (0.42 g) was evaporated to afford 2-benzoyl-4,6-dimethylpyrimidine hydrazone (391a) as a (Z)/(E)-isomer mixture (0.48 g; 100%) which formed fawn coloured plates, m.p. 112-114° (from toluene-light petroleum), ν_{max} 3360 and 3260-3120br (NH) cm^{-1}, $\delta(CDCl_3)$ 7.60-7.20 (5H, m, ArH), 6.92 and 6.84 (1H, s, H-5), 6.20-5.40 (2H, bs, NH_2) and 2.48 and 2.40 (3H, s, CH_3).

Found: C, 68.8; H, 6.2; N, 24.8%; M^+,225 (M-1).

$C_{13}H_{14}N_4$ requires: C, 69.0; H, 6.2; N, 24.8%; M, 226.

(ii) The reaction mixture from the ketone (376a) (0.43 g) was cooled and the solid deposited was combined with a second crop obtained by evaporating the filtrate to give 2-benzoyl-6-methylpyrimidin-4(3H)-one hydrazone (386a), (0.44 g; 96%) which formed colourless prisms, m.p. 194-196° (from ethanol-dimethylformamide), ν_{max} 3400, 3350, 3300 and 3220-3120 (NH), 1685 (CO) and 1660 (C=N) cm^{-1}, $\delta[(CD_3)_2SO]$ 7.60-7.10 (7H, m, ArH and 2NH), 5.99 (1H, s, H-5) and 1.98 (3H, s, CH_3)

Found: C, 63.2; H, 5.3; N, 24.8%; M^+, 228.

$C_{12}H_{12}N_4O$ requires: C, 63.1; H, 5.3; N, 24.6%; M, 228.

The Preparation of 2-Benzoylpyrimidine Phenylhydrazones

A solution of the ketone (0.002 mol) in methanol (5.0 ml) was treated with phenylhydrazine (0.002 mol) and the mixture was heated under reflux for 3 h. The reaction mixture was worked up as described for the individual reactions below.

(i) The reaction mixture from the ketone (370a) (0.42 g) was cooled and the deposited solid was combined with further material obtained by evaporating the methanolic filtrate and triturating the gummy residue with ether-b.p. 40-60° light petroleum to give 2-benzoyl-4,6-dimethylpyrimidine phenylhydrazone (391b), (total 0.47 g; 78%) which formed yellow needles, m.p. 99-100° (from ethanol), $\delta(CDCl_3)$ 7.80-7.60 (2H, m, ArH), 7.40-7.20 (3H, m, ArH), 6.90 (1H, s, H-5) and 2.50 (6H, s, CH_3).

Found: C, 76.1; H, 6.1; N, 18.5%; M^+, 302.

$C_{19}H_{18}N_4$ requires: C, 75.5; H, 6.0; N, 18.5%; M, 302.

Evaporation of the ether-light petroleum mother liquor gave a brown gum which was not further investigated.

(ii) The reaction mixture from the ketone (376a) (0.43 g) was cooled and the deposited solid collected to give a crystalline 2:1 mixture of the (E)/(Z)-isomers of 2-benzoyl-6-methylpyrimidin-4(3H)-one phenylhydrazone (386b), (0.48 g; 78%) which formed yellow needles, m.p. 254-256° (from ethanol-dimethylformamide), ν_{max} 3220-3120 (NH) and 1670 (CO) cm^{-1}, δ[$(CD_3)_2SO$] 9.60 (1H, s, NH), 7.60-7.20 (5H, m, ArH), 6.31 and 6.09 (1H, s, H-5) and 2.47 and 2.03 (3H, s, CH_3).

Found: C, 70.5; H, 5.2; N, 18.4%; M^+, 304.

$C_{18}H_{16}N_4O$ requires: C, 71.0; H, 5.3; N, 18.4%; M, 304.

Evaporation of the methanolic mother liquor gave a brown gum from which no identifiable material could be obtained.

The Attempted Reaction of 2-Benzoyl-6-methylpyrimidin-4(3H)-one Hydrazone with Triethyl Orthoformate

A suspension of the hydrazone (386a), (0.46 g, 0.002 mol) in triethyl orthoformate (5.0 ml) was heated under reflux for 1 h during which time the reaction mixture turned from colourless to deep orange. Hot-filtration of the mixture removed a solid which was combined with further crops obtained from the filtrate on cooling and on evaporation to give the unreacted hydrazone (386a) (0.32 g; 94%) which was identical (m.p. and i.r. spectrum) to an authentic sample.

The Preparation of 2-Benzoylpyrimidine N-Formylhydrazones

The hydrazone (0.002 mol) was dissolved in formic acid (5.0 ml), the solution was heated under reflux for 1 h and worked

up as described for the individual reactions below.

(i) The reaction mixture from the hydrazone (391a) (0.45 g) was evaporated and co-evaporated with toluene to give a colourless semi-solid which was washed with toluene and combined with a second crop obtained by evaporating the toluene mother liquor to afford 2-benzoyl-4,6-dimethylpyrimidine N-formylhydrazone (391c), (total 0.27 g; 54%) which formed colourless needles, m.p. 157-160° (from ethanol-b.p. 80-100° light petroleum) ν_{max} 3320 (NH) and 1730 (CO) cm^{-1}, $\delta(CDCl_3)$ 8.99 (1H, d, J10.0Hz, CH=O), 8.69 (1H, bd, J10.0Hz, NH), 7.60-7.20 (5H, m, ArH), 6.99 (1H, s, H-5) and 2.46 (6H, s, CH_3).

Found: C, M^+, 254.11794 .

$C_{14}H_{14}N_4O$ requires: C, M, 254.11675 .

A small amount of solid which was collected by hot-filtration during recrystallisation of the formylhydrazone (391c) was identified as N,N'-diformylhydrazide as colourless prisms, m.p. 158-161°C (lit.,[27] 159-160°C), (from ethanol-dimethylformamide).

Found: C, 28.0; H, 5.1; N, 31.7%; M^+, 88.

$C_2H_4N_2O_2$ requires: C, 27.3; H, 4.6; N, 31.8%; N, 88.

(ii) The reaction mixture from the hydrazone (386a) (0.46 g) was evaporated and co-evaporated with toluene to give 2-benzoyl-6-methylpyrimidin-4(3H)-one N-formylhydrazone (386c) as a 4:1 (Z)/(E)-isomer mixture (0.55 g; 100%) which formed colourless needles, m.p. 218-221° (from ethanol-dimethylformamide), ν_{max} 3120 (NH) and 1720 and 1660 (CO) cm^{-1}, $\delta[(CD_3)_2SO]$ 8.92 and 8.12 (1H, s, CH=O), 7.60-7.30 (5H, m, ArH), 6.22 and 6.19 (1H, s, H-5) and 2.09 and 2.06 (3H, s, CH_3).

Found; M^+, 256.09691 .

$C_{13}H_{12}N_4O_2$ requires: M, 256.09602 .

Repetition of the reaction for a longer time (67 h) and work-up of the mixture as described before gave the formylhydrazone (386c) in lower yield (0.23 g; 46%) together with a small amount of the ketone (376a), (0.06 g; 14%), which was identical (m.p. and i.r. spectrum) to an authentic sample, and a red gum (0.26 g) whose t.l.c. in ethyl acetate over silica showed it to be a multicomponent mixture containing both the hydrazone (386a) as well as the formylhydrazone (386c). The gum was not further investigated.

2-Benzoyl-6-methylpyrimidin-4(3H)-one N-acetyl-N-formylhydrazone (386d)

The formylhydrazone (386c), (0.26 g, 0.001 mol) was heated under reflux in acetic anhydride (5.0 ml) for 1 h, during which time the initially yellow solution turned to a deep reddish-brown colour. Evaporation and co-evaporation with toluene gave a solid residue which was washed with ether and combined with a second crop obtained by evaporating the ethereal mother liquor and triturating the residue with b.p. 40-60° light petroleum to give the N-acetyl derivative (386d), (total 0.16 g; 53%) which formed colourless rhombic crystals, m.p. 231-233° (from ethanol-dimethylformamide), ν_{max} 1735 and 1700 (CO) cm^{-1}, δ[$(CD_3)_2SO$] 8.42 (1H, s, CH=O), 7.90-7.80 (2H, m, ArH), 7.50-7.40 (3H, m. ArH), 6.50 (1H, d, J1Hz, H-5), 2.17 (3H, d, J1Hz, CH_3) and 1.15 (3H, s, CH_3).

Found: M^+, 298.10524 .

$C_{15}H_{14}N_4O_3$ requires: M, 298.10658 .

Evaporation of the light petroleum mother liquor gave a brown gum (0.14 g) from which no further identifiable material was obtained.

Attempted Cyclisation Reactions of 2-Benzoyl-6-methyl pyrimidine-4(3H)-one Formylhydrazone (386c)

(a) Using ethanolic sodium ethoxide.

A solution of the formylhydrazone (386c), (0.51 g, 0.002 mol) in absolute ethanol (15.0 ml) was treated with a solution of sodium (0.09 g, 0.004 g. atom.) in absolute ethanol (5.0 ml) and the mixture was heated under reflux for 1 h. The mixture was evaporated, treated with water (5.0 ml) and neutralised with 2M aqueous sulphuric acid and solid sodium acetate. The precipitated solid was collected to give unchanged starting-material (386c) (0.36 g; 71%) identical (m.p. and i.r. spectrum) to an authentic sample. Extraction of the aqueous mother liquor with methylene chloride yielded only a small amount of yellow gum (0.047 g) which was not investigated further.

(b) Using phosphorus oxychloride.

(i) The formylhydrazone (386c), (0.51 g, 0.002 mol) was heated under reflux with phosphorus oxychloride (10.0 ml) for 1 h during which time the yellow solution darkened rapidly. Evaporation of the mixture gave a dark brown gum which was treated with ice and filtered to remove a polymeric brown solid (0.67 g) m/e 400-500 from which no identifiable material could be obtained.

(ii) A solution of the formylhydrazone (386c), (1.02 g, 0.004 mol) in dry acetonitrile (70.0 ml) was treated in one portion with phosphorus oxychloride (4.0 ml) and the mixture was heated under reflux for 1 h. The mixture was evaporated, treated with water (20.0 ml) and extracted with methylene chloride. The organic extract was washed with 2M aqueous sodium hydroxide (2 x 5.0 ml) and evaporated to produce a brown gum

(0.51 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture.

The acidic aqueous mother liquor was neutralised with 2M aqueous sodium hydroxide and glacial acetic acid and extracted with methylene chloride to give a second brown gum (0.27 g), trituration of which with ether-methylene chloride gave a small amount of the unreacted formylhydrazone (386c), (0.09 g; 10%) identical (m.p. and i.r. spectrum) to an authentic sample. Evaporation of the ether-methylene chloride mother liquor yielded a brown gum (0.11 g) from which no identifiable material could be obtained.

(iii) The formylhydrazone (386c), (0.51 g, 0.002 mol) was dissolved in dry 1,2-dichloroethane (25.0 ml), treated with phosphorus oxychloride (1.53 g, 0.01 mol) and the mixture was heated under reflux for 2 h during which time it darkened rapidly. Evaporation of the mixture gave a brown gum which was treated with ethyl acetate and 2M aqueous sodium bicarbonate and filtered to remove inorganic material. Evaporation of the organic phase gave a brown gum (0.19 g) from which no identifiable material could be obtained.

The Manganese Dioxide Oxidation of 2-Benzoyl-4,6-dimethyl-pyrimidine Hydrazone (391a)

A solution of the hydrazone (391a), (0.45 g, 0.002 mol) in dry acetonitrile (20.0 ml) was stirred at room temperature with activated manganese dioxide (3.0 g) for 2 h. Filtration through celite and evaporation of the combined filtrate and washings obtained by extraction of the celite with boiling acetonitrile afforded 5,7-dimethyl-3-phenyl-1,2,3-triazolo-

[1,5-a]pyrimidine (392), (total 0.38 g; 85%) identical (m.p. and i.r. spectrum) to an authentic sample.

The Attempted Manganese Dioxide Oxidation of 2-Benzoyl-6-methylpyrimidin-4(3H)-one Hydrazone (386a)

The hydrazone (386a), (0.46 g, 0.002 mol) was dissolved in dry dimethylformamide (10.0 ml) and stirred at room temperature with activated manganese dioxide (3.0 g) for 2 h. Filtration through celite and evaporation of the filtrate produced a brown gum (0.57 g) which was triturated with toluene to give an intractable colourless solid (0.39 g) from which no identifiable material could be obtained.

The Reaction of 2-Benzoylpyrimidines with Toluene-p-sulphonylhydrazine

A solution of the ketone (0.002 mol) in methanol (5.0 ml) was treated with toluene-p-sulphonylhydrazine (0.37 g, 0.002 mol), the mixture was heated under reflux for 2 h and worked up as described for the individual reactions below.

(i) The reaction mixture from the ketone (370a) (0.42 g) was cooled and the deposited solid was collected to give 5,7-dimethyl-3-phenyl-1,2,3-triazolo[1,5-a]pyrimidine (392), (0.31 g; 70%) identical (m.p. and i.r. spectrum) to an authentic sample.

On standing the methanolic mother liquor deposited 2-benzoyl-4,6-dimethylpyrimidine toluene-p-sulphonylhydrazone (391e), (0.07 g; 9%) which formed fine colourless needles, m.p. 136-138° (from toluene-b.p. 80-100° light petroleum) ν_{max} 1600

(C=N) cm^{-1}, $\delta(CDCl_3)$ 7.90 (2H, dd, J2 and 8Hz, ArH), 7.60-7.20 (5H, m, ArH), 7.28 (2H, dd, J2 and 8Hz, ArH), 7.04 (1H, s, H-5), 2.53 (6H, s, CH_3) and 2.40 (3H, s, CH_3).

Found: C, 63.4; H, 5.3; N, 14.5%; M^+, 225 ($M-\underline{p}\text{-}MeC_6H_4SO_2$).

$C_{20}H_{20}N_4O_2S$ requires: C, 63.2; H, 5.3; N, 14.7%; M, 380.

(ii) The reaction mixture from the ketone (376a) (0.43 g) was cooled and the deposited solid was collected and combined with a second crop obtained by evaporating the methanolic mother liquor and triturating the residue with ether to give 6-methyl-3-phenyl-1,2,3-triazolo[1,5-a]pyrimidin-4(3H)-one (389), (total 0.29 g, 63%) identical (m.p. and i.r. spectrum) to an authentic sample.

Evaporation of the ethereal mother liquor gave an orange gum which was not further investigated.

2-Benzoyl-6-methylpyrimidin-4(3H)-one Ethoxycarbonylhydrazone (386e)

A solution of the ketone (376a), (0.43 g, 0.002 mol) in methanol (10.0 ml) was treated with ethyl carbazate (0.21 g, 0.002 mol) and toluene-p-sulphonic acid (0.02 g) and the mixture was heated under reflux for 6.5 h. The crystalline solid which separated from the mixture on cooling was collected and combined with a second crop obtained by evaporating the methanolic filtrate and triturating the resulting gum with ether to give 2-benzoyl-6-methylpyrimidin-4(3H)-one ethoxycarbonylhydrazone (386e), (total 0.48 g; 80%) which formed colourless needles, m.p. 196-199° (from ethyl acetate-ethanol), ν_{max} 3320 and 3120 (NH) and

1750 and 1680 (CO) cm^{-1}, $\delta(CDCl_3)$ 8.28 (1H, s, NH), 7.60-7.20 (5H, m, ArH), 6.25 (1H, s, H-5), 4.33 (2H, q, J7Hz, CH_2), 2.18 3H, s, CH_3) and 1.35 (3H, t, J7Hz, CH_3).

Found: C, 60.0; H, 5.5; N, 18.7%; M^+, 300.

$C_{15}H_{16}N_4O_3$ requires: C, 60.0; H, 5.4; N, 18.7%; M, 300.

Evaporation of the ethereal mother liquor gave a yellow gum (0.23 g) which was not further investigated.

The Attempted Reaction of 2-Benzoyl-4,6-dimethylpyrimidine (370a) with Ethyl Carbazate

A solution of the ketone (370a), (0.42 g, 0.002 mol) in methanol (10.0 ml) was treated with ethyl carbazate (0.21 g, 0.002 mol) and the mixture was heated under reflux for 3 h. Removal of the solvent gave an orange gum which was triturated with toluene to yield unchanged ketone (370a), (0.20 g; 47%) identical (m.p. and i.r. spectrum) to an authentic sample. Evaporation of the toluene mother liquor gave an orange gum (0.35 g) whose t.l.c. in ether over silica showed it to be a mixture of the unchanged ketone (370a) and ethyl carbazate which was not further investigated.

The Attempted Thermal Cyclisation of 2-Benzoyl-6-methyl pyrimidin-4(3H)-one Ethoxycarbonylhydrazone (386e)

(i) The ethoxycarbonylhydrazone (386e), (0.60 g, 0.002 mol) was heated under reflux in dry xylene (20.0 ml) for 12 h with provision for the distillation of any ethanol formed through a Vigreux column, dry xylene which co-distilled being replaced in the still-pot so as to maintain the volume at 10-20 ml. On cooling the mixture deposited a solid which was combined with

a second crop obtained by evaporating the mixture and triturating the residue with toluene to give unreacted starting-material (386e), (total 0.24 g; 39%) identical (m.p. and i.r. spectrum) to an authentic sample.

Evaporation of the toluene mother liquor gave a yellow gum which was crystallised from toluene-b.p. 80-100° light petroleum to give a solid (0.14 g) whose t.l.c. in ethyl acetate over silica showed it to contain two components. Treatment of the solid with 2M aqueous sodium hydroxide allowed collection of a trace amount of solid m/e 254 which could not however be further identified.

(ii) The ethoxycarbonylhydrazone (386e), (0.60 g, 0.002 mol) in dibenzyl ether (2.0 ml) was heated under reflux for 25 min during which time the initially colourless solution darkened rapidly. After cooling the mixture was diluted with ether and light petroleum to give an intractable dark green solid from which no identifiable material could be obtained.

The Attempted Reaction of 2-Benzoyl-6-methylpyrimidin-4(3H)-one Ethoxycarbonylhydrazone (386e) with Sodium Ethoxide

A solution of the ethoxycarbonylhydrazone (386e), (0.30 g, 0.002 mol) in absolute ethanol (10.0 ml) was treated with a solution of sodium (0.09 g, 0.004 g.atom) in absolute ethanol (10.0 ml) and the mixture was heated under reflux for 1 h. The mixture was evaporated, treated with water (10.0 ml) and the basic aqueous solution brought to pH 7 with concentrated hydrochloric acid and solid sodium acetate to give a colourless solid which was combined with a second crop obtained by extracting the aqueous mother liquor with methylene chloride to give unchanged

starting-material (386e) (total 0.27 g; 89%) identical (m.p. and i.r. spectrum) to an authentic sample.

The Preparation of 2-(α-Formamidobenzyl)pyrimidines

Method A

The amine (0.002 mol) was heated under reflux in formic acid (5.0 ml) for 2 h and worked up as described for the individual reactions below.

(i) The reaction mixture from the amine (371c) (0.37 g) was evaporated and co-evaporated with toluene to give a brown residue which was treated with water (5.0 ml) and extracted with methylene chloride to afford 2-(α-formamidobenzyl)pyrimidine (399c), (0.21 g; 49%) which formed colourless plates, m.p. 109-111° from toluene-light petroleum), ν_{max} 3350-3100 (NH) and 1660 (CO) cm^{-1}, δ($CDCl_3$) 8.69 (2H, d, J5Hz, H-4 and H-6), 8.35 (1H, d, J1Hz, CH=O), 8.80-8.50 (1H, br, NH), 8.50-8.00 (6H, m, H-5 and ArH) and 6.40 (1H, d, J7Hz, benzylic CH).

Found: C, 67.5; H, 5.3; N, 19.7%; M^+, 213.

$C_{12}H_{11}N_3O$ requires: C, 67.6; H, 5.2; N, 19.7%; M, 213.

(ii) The reaction mixture from the amine (371b)(0.40 g) was evaporated and co-evaporated with toluene to give a brown residue which was crystallised from toluene-ethyl acetate to give the amine (371b) formate (0.15 g; 30%) which formed fawn crystals, m.p. 142-143° (from toluene-ethyl acetate), ν_{max} 2800-2400 and 2070 ($\overset{+}{N}H_3$) and 1550 (CO_2^-), δ[$(CD_3)_2SO$] 8.60 (1H, d, J6Hz, H-6), 8.30 (1H, bs, HCO_2^-), 7.50-7.20 (6H, m, H-5 and ArH), 5.25 (1H, s, benzylic CH), 5.20-4.90 (3H, bs, $\overset{+}{N}H_3$) and 2.50 (3H, s, CH_3).

Found: C, 63.4; H, 6.2; N, 16.8%; M^+, 227 ($M-H_2O$).
$C_{13}H_{15}N_3O_2$ requires: C, 63.7; H, 6.1; N, 17.1%; M, 245.

Evaporation of the toluene-ethyl acetate mother liquor gave a dark brown gum which was crystallised from toluene-light petroleum to give 2-(α-formamidobenzyl)-4-methylpyrimidine (399b), (0.22 g; 47%) which formed fawn crystals, m.p. 134-136° (from toluene-light petroleum), ν_{max} 3230 (NH) and 1650 (CO) cm^{-1}, δ($CDCl_3$) 8.58 (1H, d, J6Hz, H-6), 8.37 (1H, s, CHO), 7.80-7.50 (1H, bd, J7.5Hz, NH), 7.5-7.1 (5H, m, ArH), 7.06 (1H, d, J6Hz, H-5), 6.36 (1H, d, J7.5Hz, benzylic CH) and 2.53 (3H, s, CH_3).

Found: C, 69.0; H, 5.9; N, 18.3%; M^+, 227.
$C_{13}H_{13}N_3O$ requires: C, 68.7; H, 5.8; N, 18.5%; M, 227.

(iii) The reaction mixture from the amine (371a) (0.43 g) was evaporated and co-evaporated with toluene to afford 4,6-dimethyl-2-(α-formamidobenzyl)pyrimidine (399a), (0.49 g; 100%) which formed colourless crystals, m.p. 162-166° (from ethyl acetate), ν_{max} 3250-3100br (NH) and 1655 (CO) cm^{-1}, δ[$(CD_3)_2SO$] 9.02 (1H, dd, J1 and 8Hz, NH), 8.16 (1H, d, J1Hz, CH=O), 7.40-7.20 (5H, m, ArH), 7.13 (1H, s, H-5), 6.11 (1H, d, J8Hz, benzylic CH) and 2.39 (6H, s, CH_3).

Found: C, 69.5; H, 5.8; N, 17.6%; M^+, 241.
$C_{14}H_{13}N_3O$ requires: C, 69.7; H, 6.2; N, 17.4%; M, 241.

(iv) The reaction mixture from the amine (372) (0.44 g) was evaporated and co-evaporated with toluene to give a brown oil (0.35 g) which was treated with water (10.0 ml) and methylene chloride and the resulting three-phase system filtered to yield 2-(α-formamidobenzyl)-6-methylpyrimidin-4(3H)-one (406a), (0.25 g; 51%) which formed colourless crystals, m.p. 215-217° (from

ethyl acetate-ethanol), ν_{max} 3300 (NH) and 1680 (CO) cm^{-1}, $\delta[(CD_3)_2SO]$ 9.05 (1H, d, J8Hz, NH), 8.14 (1H, s, CH=O), 7.50-7.30 (5H, m, ArH), 4.10 (1H, s, H-5), 5.94 (1H, d, J8Hz, benzylic CH) and 2.10 (3H, s, CH_3).

Found: C, 63.6; H, 5.3; N, 16.8%; M^+, 243.

$C_{13}H_{13}N_3O_2$ requires: C, 64.2; H, 5.4; N, 17.3%; M, 243.

Evaporation of the organic phase gave an orange gum (0.07 g) whose t.l.c. in ethyl acetate over silica showed it to be an inseparable multicomponent mixture which was not further investigated.

Method B

A solution of the amine (372) monohydrochloride, (0.50 g, 0.002 mol) in water (10.0 ml) was treated with 1M aqueous sodium hydroxide (2.0 ml) and left at room temperature for 30 min. The mixture was evaporated and co-evaporated with ethanol to give the free base which was then dissolved in formic acid (20.0 ml) and heated under reflux for 1.5h. Evaporation of the mixture and co-evaporation with toluene gave a gum which was treated with water (10.0 ml) and extracted with methylene chloride. The resulting three-phase system was filtered to yield the formamido derivative (406a), (0.38 g; 77%) identical (m.p. and i.r. spectrum) to a sample prepared in A(iv) before.

Evaporation of the separated organic phase gave only a small amount of gum (0.017 g) which was not further investigated.

The Reaction of 2-(α-Formamidobenzyl)pyrimidines with Phosphoryl Chloride

A solution of the formamido compound (0.002 mol) in dry 1,2-dichloroethane (20.0 ml) was treated with phosphoryl chloride (1.53 g, 0.01 mol) and the mixture was heated under reflux for 2 h. The mixture was evaporated, treated with ethyl acetate and 2M aqueous sodium bicarbonate and the two phase system was shaken vigorously. The organic phase was separated and evaporated and the product isolated as described for the individual reactions below.

(i) The organic phase obtained from the reaction of the formamido compound (399c) (0.42 g) was evaporated to afford 8-phenylimidazo[1,5-a]pyrimidine (402c), (0.38 g, 95%) which formed golden needles, m.p. 145-147° (from ethanol-b.p. 80-100° light petroleum), δ($CDCl_3$) 8.50-8.30 (2H, m, ArH), 8.15 (1H, dd, J2 and 4Hz, H-2), 8.05 (1H, dd, J2 and 7Hz, H-4), 7.98 (1H, s, H-6), 7.60-7.10 (3H, m, ArH) and 6.48 (1H, dd, J4 and 7Hz, H-3).

Found: C, 73.8; H, 4.7; N, 21.5%; M^+, 195.

$C_{12}H_9N_3$ requires: C, 73.8; H, 4.7; N, 21.5%; M, 195.

(ii) The organic phase obtained from the reaction of the formamido compound (399b) (0.45 g) was evaporated to give a yellow semi-solid (0.21 g) which was flash chromatographed in methylene chloride-ethyl acetate (4:1) over silica to give as the minor fraction 4-methyl-8-phenylimidazo[1,5-a]pyrimidine (402d), 0.12 g; 30%) which formed bright yellow rectangular plates, m.p. 160-163° (from toluene-b.p. 80-100° light petroleum) δ($CDCl_3$) 8.50-8.30 (2H, m, ArH), 8.16 (1H, d, J4Hz, H-2), 8.00 (1H, s, H-6), 7.60-7.10 (3H, m, ArH), 6.40 (1H, dq, J1 and 4Hz, H-3) and 2.58 (3H, d, J1Hz, CH_3)

Found: C, 74.5; H, 5.3; N, 19.8%; M^+, 209.

$C_{13}H_{11}N_3$ requires: C, 74.6; H, 5.3; N, 20.1%; M, 209.

Further elution gave the major fraction as 2-methyl-8-phenylimidazo[1,5-a]pyrimidine (402b), (0.21 g, 50%) which formed bright yellow needles, m.p. 153-155° (from toluene-b.p. 80-100° light petroleum), $\delta(CDCl_3)$ 8.50-8.30 (2H, m, ArH), 7.98 (1H, d, J8Hz, H-4), 7.93 (1H, s, H-6), 7.60-7.20 (3H, m, ArH), 6.40 (1H, d, J8Hz, H-3) and 2.55 (3H, s, CH_3).

Found: C, 74.6; H, 5.1; N, 20.0%; M^+, 209

$C_{13}H_{11}N_3$ requires: C, 74.6: H, 5.3; N, 20.1%; M, 209.

Work-up of the aqueous mother liquor gave no further material.

(iii) The organic phase obtained from the reaction of the formamido compound (399a) (0.48 g) was evaporated to afford 2,4-dimethyl-8-phenylimidazo[1,5-a]pyrimidine (402a), (0.39 g, 86%) which formed yellow plates, m.p. 158-162°, (from toluene-b.p. 80-100° light petroleum), $\delta(CDCl_3)$ 8.50-8.30 (2H, m, ArH), 7.82 (1H, s, H-6), 7.50-7.10 (3H, m, ArH), 6.18 (1H, q, J<1Hz, H-3), 2.48 (3H, s, CH_3) and 2.42 (3H, d, J<1Hz, CH_3); $\delta[(CD_3)_2SO]$ 8.40-8.30 (2H, m, ArH), 8.35 (1H, s, H-6), 7.60-7.10 (3H, m, ArH), 6.66 (1H, q, J<1Hz, H-3), 2.64 (3H, d, J<1Hz, CH_3) and 2.54 (3H, s, CH_3).

Found: C, 75.2; H, 5.9; N, 18.8%; M^+, 223.

$C_{14}H_{13}N_3$ requires: C, 75.3; H, 5.9; N, 18.8%; M, 223.

Work-up of the aqueous mother liquor gave no further material.

(iv) The organic phase obtained from the reaction of the formamido compound (406a) (0.48 g) was evaporated to give a

yellow-brown gum (0.40 g) whose t.l.c. in methylene chloride-ethyl acetate (1:1) over silica showed the presence of at least four components. Preparative t.l.c. of the gum in cyclohexane-ether (1:1) over alumina gave only 2-chloro-4-methyl-8-phenylimidazo[1,5-a]pyrimidine (407a), (0.10 g, 21%) which formed bright yellow needles, m.p. 148-150° (from b.p. 80-100° light petroleum), δ($CDCl_3$) 8.35-8.25 (2H, m, ArH), 7.94 (1H, s, H-6), 7.60-7.10 (3H, m, ArH), 6.40 (1H, q, J<1Hz, H-3) and 2.54 (3H, d, J<1Hz, CH_3).

Found: C, 64.0; H, 4.1; N, 17.3%; M^+ 245/243.
$C_{13}H_{10}ClN_3$ requires: C, 64.1; H, 4.1; N, 17.3%; M, 243.5.

2-(α-Acetamidobenzyl)-4,6-dimethylpyrimidine (400a)

A solution of the amine (371a) (0.85 g, 0.004 mol) in dry dioxane (20.0 ml) was stirred and treated in one portion with triethylamine (1.02 g, 0.01 mol). A solution of acetyl chloride (0.62 g, 0.008 mol) in dry dioxane (2.0 ml) was added dropwise and the mixture was stirred at room temperature for 1 h.

The mixture was filtered to remove the insoluble triethylamine hydrochloride and evaporated to a yellow gum which was triturated with ether to afford a solid which was combined with a second crop obtained by evaporating the ethereal mother liquor, treating the residual brown gum with 2M aqueous sodium hydroxide and methylene chloride, re-evaporation of the organic extract and trituration of the orange gum with toluene-ether to give the acetamido derivative (400a), (0.93 g; 91%) which formed colourless crystals, m.p. 121-123° (from ethyl acetate), ν_{max} 3450-3250 (NH) and 1650 (CO) cm^{-1}, δ($CDCl_3$), 7.50-7.15 (6H, m,

NH and ArH), 6.84 (1H, s, H-5), 6.18 (1H, d, J8Hz, benzylic CH), 2.40 (6H, s, CH_3) and 2.06 (3H, s, CH_3).

Found: C, 70.5; H, 6.7; N, 16.6%; M^+, 255.

$C_{15}H_{17}N_3O$ requires: C, 70.6; H, 6.7; N, 16.5%; M,255.

8-Phenyl-2,4,6-trimethylimidazo[1,5-a]pyrimidine (403a)

A solution of the acetamido derivative (400a), (0.51 g, 0.002 mol) in dry 1,2-dichloroethane (50.0 ml) was treated with phosphoryl chloride (1.53 g, 0.01 mol) and the mixture was heated under reflux for 3.5 h. The mixture was evaporated and the residue was treated with ethyl acetate and 2M aqueous sodium bicarbonate and the two phase system was shaken vigorously. Separation and evaporation of the organic phase gave 8-phenyl-2,4,6-trimethylimidazo[1,5-a]pyrimidine (403a), (0.32 g; 67%) which formed bright yellow needles, m.p. 202-204° (from ethanol-b.p. 80-100° light petroleum), $\delta(CDCl_3)$ 8.40-8.20 (2H, m. ArH), 7.50-7.10 (3H, m, ArH), 5.98 (1H, q, J<1Hz, H-3), 2.85 (3H, s, CH_3), 2.58 (3H, d, Jz1Hz, CH_3) and 2.38 (3H, s, CH_3).

Found: C, 75.6; H, 6.3; N, 17.7%; M^+, 237.

$C_{15}H_{15}N_3$ requires: C, 75.9; H, 6.4; N, 17.7%; M, 237.

Work-up of the aqueous mother liquor gave no further material.

2-(α-Acetamidobenzyl)-6-methylpyrimidin-4(3H)-one (406b)

(i) A solution of the amine (372), (0.43 g, 0.002 mol) in dry dioxane (10.0 ml) was stirred and treated dropwise with acetyl chloride (0.16 g, 0.002 mol) and the mixture was stirred at room temperature for 1 h. The mixture was filtered to give

a white solid which dissolved completely in water (5.0 ml) to give an acidic solution. Neutralisation of the solution with 2M aqueous sodium hydroxide and glacial acetic acid and extraction of the aqueous liquor with methylene chloride afforded the acetamido compound (406b), (0.19 g, 37%) which formed colourless needles, m.p. 215-218° (from ethanol-b.p. 80-100° light petroleum), ν_{max} 3300-3100br (NH) and 1690 and 1650 (CO) cm^{-1}, $\delta(CDCl_3)$ 7.50-7.10 (6H, m, NH and ArH), 6.14 (1H, s, H-5), 6.07 (1H, d, J8Hz, benzylic CH), 2.29 (3H, s, CH_3) and 2.04 (3H, s, CH_3).

Found: C, 65.2; H, 5.8; N, 16.1%; M^+, 257.
$C_{14}H_{15}N_3O_2$ requires: C, 65.4; H, 5.9; N, 16.3%; M, 257.

Evaporation of the dioxane filtrate gave no residue.

(ii) A solution of the amine (372), (0.86 g, 0.004 mol) in dry dioxane (20.0 ml) was stirred and treated with triethylamine (0.40 g, 0.004 mol). A solution of acetyl chloride (0.31 g, 0.004 mol) in dry dioxane (2.0 ml) was introduced dropwise and the mixture was stirred at room temperature for 1 h. The mixture was filtered to remove triethylamine hydrochloride and the filtrate was evaporated to give a low-melting cream solid (0.80 g) which was crystallised from ethanol-b.p. 80-100° light petroleum to afford the pure acetamido compound (406b), (0.33 g; 32%) identical (m.p. and i.r. spectrum) to a sample obtained previously. Evaporation of the ethanol-light petroleum mother liquor produced an oil (0.34 g) whose i.r. spectrum exhibited carbonyl absorption at 1745 cm^{-1}. T.l.c. of the oil in ethyl acetate over silica showed it to contain three components, the major product being the acetamido product (406b). The component displaying ester i.r. carbonyl absorption at 1745 cm^{-1}

is probably the O,N-diacetyl derivative (405b). The oil was not further investigated.

(iii) A solution of the amine (372), (0.43 g, 0.002 mol) in glacial acetic acid (10.0 ml) was heated under reflux for 1 h. Evaporation and co-evaporation with toluene afforded the acetamido derivative (406b), (0.49 g; 96%) identical (m.p. and i.r. spectrum) to an authentic sample.

The Reaction of 2-(α-Acetamidobenzyl)-6-methylpyrimidin-4(3H) one (406b) with Phosphoryl Chloride

A solution of the acetamide (406b), (0.45 g, 0.002 mol) in dry 1,2-dichloroethane (25.0 ml) was treated with phosphoryl chloride (1.3 g, 0.009 mol) and the mixture was heated under reflux for 3 h. The solvent was removed and the residue was treated with ethyl acetate and 2M aqueous sodium bicarbonate. After shaking vigorously the two phase system was separated and the organic phase was evaporated to give a yellow solid (0.26 g) whose t.l.c. in ethyl acetate over silica showed it to contain two components. Flash chromatography of the mixture eluting with cyclohexane-ethyl acetate (1:1) gave as the minor component 4-chloro-2,6-dimethyl-8-phenylimidazo[1,5-a]pyrimidine (407d), (0.04 g; 8%) which formed yellow needles, m.p. 160-162° (from b.p. 80-100° light petroleum), δ($CDCl_3$) 8.35-8.20 (2H, m, ArH), 7.45-7.15 (3H, m, ArH), 6.38 (1H, s, H-3), 2.96 (3H, s, CH_3) and 2.42 (3H, s, CH_3).

Found: C, 64.6; H, 4.7; N, 16.0%; M^+, 259/257.
$C_{14}H_{12}ClN_3$ requires: C, 65.2; H, 4.7; N, 16.3%; M, 257.5.

Further elution gave as the major component 2-chloro-4,6-dimethyl-8-phenylimidazo[1,5-a]pyrimidine (407c), (0.18 g; 48%)

which formed yellow needles, m.p. 220-222° (from ethanol-b.p. 80-100° light petroleum), δ($CDCl_3$) 8.35-8.20 (2H, m, ArH), 7.55-7.20 (3H, m, ArH), 6.17 (1H, q, J1Hz, H-3), 2.90 (3H, s, CH_3) and 2.69 (3H, d, J1Hz, CH_3).

Found: C, 64.6; H, 4.7; N, 16.2%; M^+, 259/257.
$C_{14}H_{12}ClN_3$ requires: C, 65.2; H, 4.7; N, 16.3%; M, 257.5.

The Preparation of 2-(α-Benz amidobenzyl)pyrimidines

A solution of the amine (0.002 mol) in dry dioxane (10.0 ml) was stirred and treated in one portion with triethylamine (0.20 g, 0.002 mol) followed dropwise with a solution of benzoyl chloride (0.28 g, 0.002 mol) in dry dioxane (2.0 ml). The mixture was stirred at room temperature for 1 h and worked up as described for the individual reactions below.

(i) The reaction mixture from the amine (371c) (0.38 g) was filtered to remove triethylamine hydrochloride and the filtrate was evaporated to afford after crystallisation 2-(α-benzamidobenzyl)pyrimidine (401c), (0.47 g; 82%) which formed colourless needles, m.p. 179-181° (from toluene), ν_{max} 3390 (NH) and 1670 (CO) cm^{-1}, δ($CDCl_3$) 8.75 (2H, d, J6Hz, H-4 and H-6), 8.25 (1H, bd, J8Hz, NH), 8.00-7.90 (2H, m, ArH), 7.60-7.10 (8H, m, ArH), 7.23 (1H, t, J6Hz, H-5) and 6.48 (1H, d, J8Hz, benzylic CH).

Found: M^+, 289.12324 .
$C_{18}H_{15}N_3O$ requires: M, 289.12159 .

(ii) The reaction mixture from the amine (371b), (0.40 g) was filtered to remove triethylamine hydrochloride and the filtrate was evaporated to give 2-(α-benzamidobenzyl)-4-methylpyrimidine (401b), (0.59 g, 97%) which formed colourless crystals, m.p. 140-141° (from toluene), ν_{max} 3380 (NH) and 1650 (CO) cm^{-1},

$\delta(CDCl_3)$ 8.56 (1H, d, J5Hz, H-6), 8.25 (1H, d, J7Hz, NH), 7.97-7.85 (2H, m, ArH), 7.57-7.19 (8H, m, ArH), 7.04 (1H, d, J5Hz, H-5), 6.42 (1H, d, J7Hz, benzylic CH) and 2.54 (3H, s, CH_3).

Found: C, 75.4; H, 5.5; N, 13.9%; M^+, 303.

$C_{19}H_{17}N_3O$ requires: C, 75.3; H, 5.6; N, 13.9%; M, 303.

(iii) The reaction mixture from the amine (371a) (0.42 g) was filtered to remove triethylamine hydrochloride and the filtrate was evaporated to give a fawn semi-solid which was triturated with ether to afford 2-(α-benzamidobenzyl)-4,6-dimethylpyrimidine (401a), (0.53 g; 84%) which formed colourless needles, m.p. 171-173° (from toluene), ν_{max} 3430 (NH) and 1655 (CO) cm^{-1}, $\delta(CDCl_3)$ 8.31 (1H, d, J7Hz, NH), 7.95-7.80 (2H, m, ArH), 7.58-7.16 (8H, m, ArH), 6.86 (1H, s, H-5), 6.37 (1H, d, J7Hz, benzylic CH) and 2.42 (6H, s, CH_3).

Found: C, 76.0; H, 5.9; N, 13.4%; M^+, 317.

$C_{20}H_{19}N_3O$ requires: C, 75.7; H, 6.0; N, 13.2%; M, 317.

Evaporation of the ethereal trituration liquor gave an orange oil (0.27 g) from which no identifiable material could be obtained.

(iv) The reaction mixture from the amine (372) (0.43 g) was filtered to remove triethylamine hydrochloride and the filtrate was evaporated to give a fawn gum which was triturated with toluene to afford 2-(α-benzamidobenzyl)-6-methylpyrimidin-4(3H)-one (406c), (0.45 g; 70%) which formed fine colourless needles, m.p. 221-222° (from toluene-ethanol), ν_{max} 3400 (NH) and 1690 and 1650 (CO) cm^{-1}, $\delta[(CD_3)_2SO]$ 9.80-9.60 (1H, bs, NH), 9.03 (1H, d, J2.5Hz, NH), 8.00-7.90 (2H, m, ArH), 7.60-7.30 (8H, m, ArH), 6.10 (1H, s, H-5), 6.08 (1H, d, J2.5Hz, benzylic

CH) and 2.18 (3H, s, CH_3).

Found: C, 71.2; H, 5.5; N, 13.2%; M^+, 319.

$C_{19}H_{17}N_3O_2$ requires: C, 71.5; H, 5.4; N, 13.2%; M, 319.

Evaporation of the toluene mother liquor gave a fawn solid (0.14 g) whose t.l.c. in ethyl acetate over silica showed it to be a two component mixture containing the benzamide (406c) as one of the components. The solid was heated to boiling in ethanol and hot-filtered to remove the dibenzoyl derivative 2-(α-benzamidobenzyl)-4-O-benzoyl-6-methylpyrimidine (405c), (0.05 g; 6%) which formed colourless needles, m.p. 186-188° (from ethanol), ν_{max} 3390 (NH) and 1745 and 1655 (CO) cm^{-1}, δ[$(CD_3)_2SO$] 9.24 (1H, d, J2Hz, NH), 8.20-8.10 (2H, m, ArH), 8.00-7.90 (2H, m, ArH), 7.90-7.25 (12H, m, H-5 and ArH), 6.38 (1H, d, J2Hz, benzylic CH) and 2.55 (3H, s, CH_3).

Found: C, 73.8; H, 4.9; N, 9.8%; M^+, 423.

$C_{26}H_{21}N_3O_3$ requires: C, 73.8; H, 5.0; N, 9.9%; M, 423.

On cooling the ethanolic filtrate deposited a small amount of the benzamide (406c), (0.04 g; total 76%). Evaporation of the ethanol mother liquor gave a pink gum (0.06 g) which was not further investigated.

The Reaction of 2-(α-Benzamidobenzyl)pyrimidines with Phosphoryl Chloride

A solution of the benzamido compound (0.002 mol) in dry 1,2-dichloroethane (50.0 ml) was treated with phosphoryl chloride (1.53 g, 0.01 mol) and the mixture was heated under reflux for 3-8 h. In some cases pyridine (0.5 ml) was added during the reaction to neutralise the HCl produced. The mixture was evaporated, treated with ethyl acetate and 2M aqueous sodium bicarbonate and the two phase system was shaken vigorously.

The organic phase was separated and evaporated and the product isolated as described for the individual reactions below.

(i) The organic phase obtained from the reaction of the benzamido compound (401c) (0.58 g), which had been refluxed for 7.5 h and to which pyridine had been added after 1 h, was evaporated to give an orange solid (0.51 g) which was flash chromatographed in cyclohexane-ethyl acetate (3:1) over silica to afford 6,8-diphenylimidazo[1,5-a]pyrimidine (404c), (0.27 g; 50%) which formed bright yellow needles, m.p. 150-152° (from light petroleum), δ($CDCl_3$) 8.50-8.40 (2H, m, ArH), 8.45 (1H, dd, J1.5 and 7.5Hz, H-4), 8.12 (1H, dd, J1.5 and 3.5Hz, H-2), 7.90-7.80 (2H, m, ArH), 7.60-7.40 (5H, m, ArH), 7.35-7.25 (1H, m, ArH) and 6.39 (1H, dd, J3.5 and 7.5Hz, H-3).

Found: C, 79.6; H, 4.8; N, 15.3%; M^+, 271.

$C_{18}H_{13}N_3$ requires: C, 79.7; H, 4.8; N, 15.5%; M, 271.

followed by unchanged starting-material (401c) (0.21 g; 36%) identical (m.p. and i.r. spectrum) to an authentic sample.

(ii) The organic phase obtained from the reaction of the benzamido compound (401b) (0.61 g), which had been refluxed for 5 h and to which pyridine had been added after 3 h, was evaporated to give an orange semi-solid (0.58 g) which was flash chromatographed over silica. Elution with cyclohexane-ethyl acetate (1:1) gave a yellow solid (0.25 g) which was t.l.c. pure and which analysed correctly for the molecular formula $C_{19}H_{15}N_3$.

Found: C, 79.8; H, 5.3; N, 14.6%; M^+, 285.

$C_{19}H_{15}N_3$ requires: C, 80.0; H, 5.3; N, 14.7%; M, 285.

The solid was shown by ^1H n.m.r. spectroscopy to be an inseparable 2:1 mixture of the isomeric 2-methyl-6,8-diphenylimidazo[1,5-a]pyrimidine (404b) and 4-methyl-6,8-diphenylimidazo[1,5-a]pyrimidine (404d) (0.25 g; total 44%). The superimposed ^1H

n.m.r. spectra are (i) 2-methyl isomer δ($CDCl_3$) 8.55-8.39 (2H, m, ArH), 8.33 (1H, d, J7Hz, H-4), 7.60-7.20 (8H, m, ArH), 6.43 (1H, d, J7Hz, H-3) and 2.57 (3H, s, CH_3), and (ii) 4-methyl isomer δ($CDCl_3$) 8.12 (1H, d, J4Hz, H-2), 7.87-7.74 (2H, m, ArH), 7.60-7.20 (8H, m, ArH), 6.31 (1H, dq, J1 and 4Hz, H-3) and 2.13 (3H, d, J1Hz, CH_3).

Elution with ethyl acetate gave unchanged starting-material (0.35 g; 56%) identical (m.p. and i.r. spectrum) to an authentic sample.

(iii) The organic phase obtained from the reaction of the benzamido compound (401a) (0.63 g), which had been refluxed for 8 h and to which pyridine had been added after 2 h, was evaporated to give a yellow solid (0.54 g) whose t.l.c. in ethyl acetate over silica showed it to contain two components. Separation of the mixture by preparative t.l.c. in methylene chloride-ether (9:1) over silica afforded as the less polar minor component 2,4-dimethyl-6,8-diphenylimidazo[1,5-a]pyrimidine (404a), (0.14 g; 23%) which formed bright yellow needles, m.p. 190-193° (from toluene-b.p. 80-100° light petroleum), δ($CDCl_3$) 8.50-8.40 (2H, m, ArH), 7.60-7.20 (8H, m, ArH), 6.19 (1H, q, J<1Hz, H-3), 2.51 (3H, s, CH_3) and 2.08 (3H, d, J<1Hz, CH_3).

Found: M^+, 299.14283 .
$C_{20}H_{17}N_3$ requires: M, 299.14224 .

The major component was identified as unchanged starting-material (0.24 g; 39%) identical (m.p. and i.r. spectrum) to an authentic sample.

(iv) The organic phase obtained from the reaction of the benzamido compound (406c) (0.59 g), which had been refluxed for 3 h, was evaporated to give a yellow solid (0.53 g) which was

t.l.c. pure and which analysed for the molecular formula $C_{19}H_{14}ClN_3$.

Found: C, 72.0; H, 4.5; N, 13.2%; M^+, 321/319.

$C_{19}H_{14}ClN_3$ requires: C, 71.4; H, 4.4; N, 13.2%; M, 319.5.

The solid was shown by ^1H n.m.r. spectroscopy to be an inseparable 3:1 mixture of the isomeric 2-chloro-6,8-diphenyl-4-methylimidazo[1,5-a]pyrimidine (407e) and 4-chloro-6,8-diphenyl-2-methylimidazo[1,5-a]pyrimidine (407f), (0.53 g; total 90%). The superimposed ^1H n.m.r. spectra are (i) 2-chloro-4-methyl isomer $\delta(CDCl_3)$ 8.41-8.36 (2H, m, ArH), 7.58-7.25 (8H, m, ArH), 6.33 (1H, q, J1Hz, H-3) and 2.11 (3H, d, J1Hz, CH_3) and (ii) 4-chloro-2-methyl isomer $\delta(CDCl_3)$ 8.48-8.44 (2H, m, ArH), 7.58-7.25 (8H, m, ArH), 6.54 (1H, s, H-3) and 2.57 (3H, s, CH_3).

4,6-Dimethyl-2-(α-N-methylcarbamoylaminobenzyl)pyrimidine (408a)

A solution of the amine (371a), (0.85 g, 0.004 mol) in dry acetonitrile (10.0 ml) was treated with methyl isocyanate (0.23 g, 0.004 mol) and the mixture was left at room temperature for 24 h during which time a colourless solid was deposited. This was collected and combined with further material obtained by evaporating the filtrate and triturating the resulting gum with ether to give the urea (408a), (total 0.97 g; 90%) which formed colourless needles, m.p. 217-218° (from ethyl acetate-ethanol), ν_{max} 3345-3320 (NH) and 1630 (CO) cm^{-1} $\delta(CDCl_3)$ 7.45-7.40 (2H, m, ArH), 7.30-7.10 (3H, m, ArH), 6.92 (1H, s, H-5), 6.85 (1H, d, J8Hz, benzylic CH), 6.07 (2H, d and q, J6 and 8Hz, 2NH), 2.68 (3H, d, J6Hz, N-CH_3) and 2.43 (6H, s, $2CH_3$).

Found: C, 66.4; H, 6.8; N, 20.8%; M^+, 270.

$C_{15}H_{18}N_4$ requires: C, 66.6; H, 6.7; N, 20.7%; M, 270.

2,4-Dimethyl-6-methylamino-8-phenylimidazo[1,5-a]pyrimidine (410a)

A solution of the N-methylurea (408a) (0.68 g, 0.003 mol) in dry 1,2-dichloroethane (50.0 ml) was treated with phosphoryl chloride (2.0 g, 0.013 mol) and the mixture was heated under reflux for 0.5 h during which time an orange solid precipitated. The mixture was evaporated, treated with ethyl acetate and 2M aqueous sodium bicarbonate and mixed vigorously. Separation of the two phase system and evaporation of the organic layer afforded the methylamino-imidazopyrimidine (410a), (0.66 g; 100%) which formed bright red needles, m.p. 229-232° (from toluene-b.p. 80-100° light petroleum) ν_{max} 3380 (NH) cm^{-1}, $\delta(CDCl_3)$ 8.40-8.30 (2H, m, ArH), 7.60-7.10 (3H, m, ArH), 5.70 (1H, s, H-3), 3.80 (1H, bs, NH), 3.00 (3H, bs, N-CH_3), 2.50 (3H, s, CH_3) and 2.30 (3H, s, CH_3).

Found: C, 71.4; H, 6.4; N, 22.2%; M^+, 252.

$C_{15}H_{16}N_4$ requires: C, 71.4; H, 6.4; N, 22.2%; M, 252.

6-Methyl-2-(α-N-methylcarbamoylaminobenzyl)pyrimidin-4(3H)-one (411a).

A solution of the amine (372), (0.43 g, 0.002 mol) in dry dioxane (20.0 ml) was treated with methyl isocyanate (0.12 g, 0.002 mol) and the mixture was left at room temperature for 3 h during which time a colourless solid separated. The mixture was filtered to give the urea (411a), (0.39 g; 71%) which formed colourless crystals, m.p. 225-226° (from methanol-dimethylformamide), ν_{max} 3400, 3380 and 3260 (NH) and 1690 and 1640 (CO) cm^{-1}, $\delta[(CD_3)_2SO]$ 7.40-7.25 (5H, m, ArH), 6.68 (1H, d, J2Hz, NH), 6.20 (1H, q, J1Hz, NH), 60.5 (1H, s, H-5), 5.75 (1H, d, J2Hz, benzylic CH), 2.56 (3H, d, J1Hz, N-CH_3) and 2.19 (3H,

s, CH_3).

Found: C, 61.7; H, 6.1; N, 20.8%; M^+, 272.

$C_{14}H_{16}N_4O_2$ requires: C, 61.8; H, 5.9; N, 20.6%; M, 272.

Evaporation of the filtrate gave a yellow gum (0.15 g) whose t.l.c. in ethyl acetate over silica showed it to be an inseparable multicomponent mixture which was not further investigated.

The Attempted Reaction of 6-Methyl-2-(α-N-methylcarbamoyl-aminobenzyl)pyrimidin-4(3H)-one (411a) with Phosphoryl Chloride

A suspension of the N-methylurea (411a), (0.54 g, 0.002 mol) in dry 1,2-dichloroethane (25.0 ml) was treated with phosphoryl chloride (1.53 g, 0.01 mol) and the mixture was heated under reflux for 1.5 h during which time the suspended solid dissolved to give a crimson solution. The solvent was removed and the residue was treated with ethyl acetate and 2M aqueous sodium bicarbonate. After vigorous mixing the two phase system was separated and the organic phase was evaporated to give a crimson glass (0.43 g) whose t.l.c. in methylene chloride over silica showed it to be an inseparable multicomponent mixture from which no identifiable material could be obtained.

4,6-Dimethyl-2-(α-N-phenylcarbamoylaminobenzyl)pyrimidine (408b)

A solution of the amine (371a), (0.21 g, 0.001 mol) in dry acetonitrile (10.0 ml) was treated with phenyl isocyanate (0.119 g, 0.001 mol) and the mixture was allowed to stand at room temperature for 22 h. The precipitated solid was collected

and combined with further material obtained by evaporating the filtrate to yield the urea (408b), (total 0.31 g, 93%) which formed colourless crystals, m.p. 217-219° (from ethanol-b.p. 80-100° light petroleum), ν_{max} 3300, 3200 and 3150 (NH) and 1660 (CO) cm^{-1}, $\delta[(CD_3)_2SO]$ 8.96 (1H, s, NH), 7.50-7.20 (10H, m, ArH), 7.12 (1H, s, H-5), 6.89 (1H, bd, J7Hz, NH), 5.96 (1H, d, J7Hz, benzylic CH) and 2.40 (6H, s, $2CH_3$).

Found: M^+, 332.16152 .

$C_{20}H_{20}N_4O$ requires: M, 332.16370 .

6-Anilino-2,4-dimethyl-8-phenylimidazo[1,5-a]pyrimidine (410b)

A solution of the phenylurea (408b), (0.66 g, 0.002 mol) in dry 1,2-dichloroethane (50.0 ml) was treated with phosphoryl chloride (1.53 g, 0.01 mol) and the mixture was heated under reflux for 2 h with the addition of pyridine (0.25 ml) after 1 h to neutralise the HCl produced. Removal of the solvent gave a red-brown residue which was treated with ethyl acetate and 2M aqueous sodium bicarbonate. After shaking vigorously the two phase system was separated and the organic layer was evaporated to give the anilino-imidazopyrimidine (410b), (0.62 g; 98%) which formed yellow cubes, m.p. 213-217° (from toluene), ν_{max} 3400-3250br (NH) cm^{-1}, $\delta(CDCl_3)$ 8.40-8.20 (2H, m, ArH), 7.50-6.40 (9H, m, NH and ArH), 6.09 (1H, q, J<1Hz, H-3), 2.57 (3H, d, J<1Hz, CH_3) and 2.44 (3H, s, CH_3).

Found: C, 76.1; H, 6.0; N, 17.9%; M^+, 314.

$C_{20}H_{18}N_4$ requires: C, 76.4; H, 5.8; N, 17.8%; M, 314.

6-Methyl-2-(α-N-phenylcarbamoylaminobenzyl)pyrimidin-4(3H)-one (411b)

A solution of the amine (372), (0.43 g, 0.002 mol) in dry dioxane (20.0 ml) was treated with phenyl isocyanate (0.24 g, 0.002 mol) and the mixture was left at room temperature for 21 h. Filtration afforded the urea (411b), (0.59 g; 88%) which formed colourless crystals, m.p. 215-217° (from ethanol-dimethylformamide), ν_{max} 3350 and 3300 (NH) and 1690 and 1660 (CO) cm^{-1}, δ[$(CD_3)_2SO$] 8.95 (1H, s, NH), 7.50-7.10 (10H, m, NH and ArH), 7.00-6.85 (1H, m, ArH), 6.08 (1H, s, H-5), 5.80 (1H, d, J8Hz, benzylic CH) and 2.18 (3H, s, CH_3).

Found: M^+, 334.14162 .
$C_{19}H_{18}N_4O_2$ requires: M, 334.14297 .

Evaporation of the filtrate gave a yellow gum (0.15 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

The Attempted Reaction of 6-Methyl-2-(α-N-phenylcarbamoylaminobenzyl)pyrimidin-4(3H)-one (411b) with Phosphoryl Chloride

A suspension of the N-phenylurea (411b), (0.67 g, 0.002 mol) in dry 1,2-dichloroethane (50.0 ml) was treated with phosphoryl chloride (1.53 g, 0.01 mol) and the mixture was heated under reflux for 3 h. The solvent was removed and the residue was treated with ethyl acetate and 2M aqueous sodium bicarbonate. After vigorous mixing the organic layer was separated and evaporated to yield a yellow gum (0.50 g) whose t.l.c. in ethyl acetate over silica showed the presence of two components. Flash chromatography in ethyl acetate over silica, however, gave

only a brown glass (0.29 g) whose ^{1}H n.m.r. spectrum showed it to be a complex mixture which was not further investigated.

6-Amino-2,4-dimethyl-8-phenylimidazo[1,5-a]pyrimidine (410c)

(i) A solution of the amine (371a), (0.43g,0.002 mol) in methanol (10.0 ml) was treated with a solution of cyanogen bromide (0.53 g, 0.005 mol) in methanol (5.0 ml) and the mixture was stirred at room temperature for 2 h. Filtration afforded the hydrobromide of 6-amino-2,4-dimethyl-8-phenylimidazo[1,5-a]-pyrimidine (410c), (0.14 g; 21%) which formed yellow needles, m.p. 232-235° (from ethanol-dimethylformamide), ν_{max} 3440, 3290 and 3140 (NH) cm^{-1}, δ[$(CD_3)_2SO$] 8.10-8.00 (2H, m, ArH), 7.60-7.35 (3H, m, ArH), 6.44 (1H, q, J<1Hz, H-3), 2.76 (3H, d, J<1Hz, CH_3) and 2.36 (3H, s, CH_3).

Found: C, 53.2; H, 4.7; N, 17.2%; M^+, 238 (M-HBr).
$C_{14}H_{15}BrN_4$ requires: C, 52.7; H, 4.7; N, 17.5%; M, 319.

The filtrate was evaporated, basified with 1M aqueous sodium hydroxide and extracted with methylene chloride to give a yellow gum which was triturated with ether to yield 6-amino-2,4-dimethyl-8-phenylimidazo[1,5-a]pyrimidine (410c), (0.09 g; 18%) which formed orange needles, m.p. 214-215° (from ethanol-dimethylformamide), ν_{max} 3440, 3290 and 3130 (NH) cm^{-1}, δ[$(CD_3)_2SO$] 8.30-8.15 (2H, m, ArH), 7.45-7.00 (3H, m, ArH), 6.11 (1H, q, J1Hz, H-3), 5.54 (2H, bs, NH_2), 2.74 (3H, d, J1Hz, CH_3) and 2.30 (3H, s, CH_3).

Found: C, 70.5; H, 6.1; N, 23.8%; M^+, 238.
$C_{14}H_{14}N_4$ requires: C, 70.6; H, 5.9; N, 23.5%; M, 238.

Evaporation of the ethereal mother liquor gave a yellow gum (0.23 g) whose t.l.c. in ethyl acetate over silica showed it to be a multicomponent mixture containing more of the amine (410c). The gum was not further investigated.

(ii) The reaction of the amine (371a) with cyanogen bromide was repeated as described in (i) and the solid containing mixture was evaporated, treated with 1M aqueous sodium hydroxide and shaken well. Extraction with methylene chloride gave an orange gummy solid (0.43 g) which was triturated with ether to afford the amine (410c), (0.25 g; 52%) identical (m.p. and i.r. spectrum) to a sample prepared in (i) before.

Evaporation of the ethereal mother liquor gave an orange gum (0.10 g) whose t.l.c. in methylene chloride over silica showed it to be a multicomponent mixture which was not further investigated.

6-Amino-8-phenylimidazo[1,5-a]pyrimidine (410d)

A solution of the amine (371c), (0.37 g, 0.002 mol) in methanol (10.0 ml) was treated with a solution of cyanogen bromide (0.53 g, 0.005 mol) in methanol (5.0 ml) and the mixture was stirred at room temperature for 2 h. The mixture was evaporated, treated with 1M aqueous sodium hydroxide (20.0 ml) and extracted with methylene chloride to give a red gum (0.39 g). Flash chromatography of the gum eluting with cyclohexane-ethyl acetate (2:1) yielded 6-amino-8-phenylimidazo[1,5-a]-pyrimidine (410d), (0.18 g; 42%) which formed crimson needles, m.p. 177-178° (from ethanol-water), ν_{max} 3700-3200br (NH) cm^{-1}, δ[$(CD_3)_2SO$] 8.30-8.10 (3H, m, H-4 and ArH), 7.89 (1H, dd, J2 and 4Hz, H-2), 7.50-7.00 (3H, m, ArH), 6.47 (1H, dd, J4 and 7Hz, H-3) and 6.22 (2H, bs, NH_2).

Found: M^+, 210.09048 .

$C_{12}H_{10}N_4$ requires: M, 210.09054 .

Elution with methanol gave no further material.

The Preparation of Imidazo[1,5-a]pyrimidin-6(7H)-thiones

A solution of the amine (0.002 mol) in dry toluene (10.0 ml) was treated with carbon disulphide (4.0 ml), heated under reflux for 17 h and worked up as described for the individual reactions below.

(i) The reaction mixture from the amine (371c) (0.37 g) was cooled and the red crystalline precipitate was collected to afford 8-phenylimidazo[1,5-a]pyrimidin-6(7H)-thione (418c), (0.46 g, 100%) which formed bright red needles, m.p. 250-255° (from methanol-dimethylformamide), δ[$(CD_3)_2SO$] 8.42 (1H, dd, J2 and 8Hz, H-4), 8.16 (1H, dd, J2 and 4Hz, H-2), 8.20-8.00 (2H, m, ArH), 7.60-7.10 (3H, m, ArH) and 6.74 (1H, dd, J4 and 8Hz, H-3).

Found: M^+, 227.05065 .

$C_{12}H_9N_3S$ requires: M, 227.05171 .

The organic mother liquor was evaporated to give no residue.

(ii) The reaction mixture from the amine (371b) (0.40 g) was cooled and the precipitated solid was collected to give 2-methyl-8-phenylimidazo[1,5-a]pyrimidin-6(7H)-one (418b), (0.39 g; 81%) which formed bright red needles, m.p. 268-271° (from methanol-dimethylformamide), δ[$(CD_3)_2SO$] 11.80-11.00 (1H, bs, NH), 8.33 (1H, d, J7.5Hz, H-4), 8.20-8.00 (2H, m, ArH), 7.45-7.30 (3H, m, ArH), 6.63 (1H, d, 7.5Hz, H-3) and 2.43 (3H, s, CH_3).

Found: C, 64.6; H, 4.6; N, 17.4%; M^+, 241.

$C_{13}H_{11}N_3S$ requires: C, 64.7; H, 4.6; N, 17.4%; M, 241.

Evaporation of the organic mother liquor gave a red oil (0.06 g) whose t.l.c. in ethyl acetate over silica showed it to be a multicomponent mixture which was not investigated further.

(iii) The reaction mixture from the amine (371a) (0.43 g) was cooled and the precipitated solid was collected to yield 4,6-dimethyl-8-phenylimidazo[1,5-a]pyrimidin-6(7H)-thione (418a), (0.43 g, 85%) which formed bright orange needles, m.p. 257-259° (from ethanol-dimethylformamide), δ[$(CD_3)_2SO$] 8.20-8.00 (2H, m, ArH), 7.50-7.10 (3H, m, ArH), 6.20 (1H, s, H-3), 3.09 (3H, s, CH_3) and 2.27 (3H, s, CH_3).

Found: C, 65.9; H, 5.1; N, 16.6%; M^+, 255.

$C_{14}H_{13}N_3S$ requires: C, 65.9; H, 5.1; N, 16.5%; M, 255.

Evaporation of the filtrate yielded a red oil which was triturated with ether to give N,N'-di-[α-(4,6-dimethylpyrimid-2-yl)benzyl]thiourea (419a), (0.02 g; 4%) which formed cream crystals, m.p. 229-230° (from ethanol-dimethylformamide-b.p. 80-100° light petroleum), ν_{max} 3350 cm^{-1}.

Found: M^+, 436.23708 .

$C_{27}H_{28}N_6S$ requires: M, 436.23753 .

Evaporation of the ethereal mother liquor gave a dark gum which was not further investigated.

(iv) The reaction mixture from the amine (372) (0.43 g) was filtered to remove a yellow solid (0.44 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multi-component mixture which was also confirmed by its complex ^1H n.m.r. spectrum. Evaporation of the filtrate gave only a yellow gum (0.07 g) whose t.l.c. in ethyl acetate over silica

showed it also to be a complex mixture. The solid and the gum were not investigated further.

2,4-Dimethyl-6-methylthio-8-phenylimidazo[1,5-a]pyrimidine (420a)

A suspension of the thione (418a), (0.51 g, 0.002 mol) in Analar acetone (50.0 ml) was treated with anhydrous potassium carbonate (1.5 g) and dimethyl sulphate (10 ml) and the mixture was heated under reflux for 4 h. The mixture was evaporated, treated with water (20.0 ml) and filtered to afford 2,4-dimethyl-6-methylthio-8-phenylimidazo[1,5-a]pyrimidine (420a), (0.52 g; 96%) which formed bright orange rhombic crystals, m.p. 164-167° (from ethanol-b.p. 80-100° light petroleum), $\delta(CDCl_3)$ 8.50-8.30 (2H, m, ArH), 7.50-7.10 (3H, m, ArH), 6.00 (1H, q, J<1Hz, H-3), 2.80 (3H, d, J<1Hz, CH_3), 2.69 (3H, s, 5-CH_3) and 2.39 (3H, s, CH_3).

Found: C, 66.8; H, 5.5; N, 15.7%; M^+, 269.
$C_{15}H_{15}N_3S$ requires: C, 66.9; H, 5.6; N, 15.6%; M, 269.

Work-up of the aqueous mother liquor gave no further material.

The Attempted Reaction of 2,4-Dimethyl-6-methylthio-8-phenylimidazo[1,5-a]pyrimidine (420a) with Hydrazine Hydrate

A solution of the thiomethyl-compound (420a), (0.16 g, 0.0006 mol) in absolute ethanol (10.0 ml) was treated with hydrazine hydrate (0.15 ml) and the mixture was left at room temperature for 17 h. The t.l.c. of the solution in methylene chloride over silica showed that no reaction had taken place

and so the mixture was heated under reflux for 2 h. An additional portion of hydrazine hydrate (0.20 ml) was added and heating was continued for a further 2 h. On cooling the reaction mixture deposited unchanged starting-material (420a) (0.13 g; 77%) identical (m.p. and i.r. spectrum) to an authentic sample.

Evaporation of the mother liquor gave an orange semi-solid (0.05 g) whose t.l.c. in methylene chloride over silica showed it to be largely starting-material and therefore it was not further investigated.

The Attempted Reaction of 2,4-Dimethyl-6-methylthio-8-phenylimidazo[1,5-a]pyrimidine (420a) with Ethanolic Sodium Ethoxide

A solution of the thiomethyl-compound (420a) (0.54 g, 0.002 mol) in absolute ethanol (10.0 ml) was treated with a solution of sodium (0.09 g, 0.008 g atom) in absolute ethanol (10.0 ml) and the mixture was heated under reflux for 5 h. The mixture was evaporated, treated with water (15.0 ml), neutralised with 2M aqueous hydrochloric acid and solid sodium acetate and filtered to give unchanged starting-material (420a) (0.52 g; 97%) identical (m.p. and i.r. spectrum) to an authentic sample.

The Preparation of Ethyl N-[α-(Pyrimid-2-yl)benzyl]carbamates

Method A

A solution of the amine (0.002 mol) in dry dioxane (10.0 ml) was stirred and treated with triethylamine (0.51 g, 0.005 mol) in one portion. A solution of ethyl chloroformate (0.24 g, 0.0022 mol) in dry dioxane (1.0 ml) was added dropwise, the

mixture was stirred at room temperature for 1 h and worked up as described for the individual reactions below.

(i) The reaction mixture from the amine (371c) (0.37 g) was filtered to remove triethylamine hydrochloride, and the filtrate was evaporated. The residue was treated with water (5.0 ml) and extracted with methylene chloride to afford a red oil (0.51 g) which was triturated with ether to afford a fawn solid. This was combined with a second crop obtained by evaporating the ethereal filtrate to give ethyl N-[α-(pyrimid-2-yl)benzyl]carbamate (425c) (total 0.21 g; 61%) which formed colourless crystals, m.p. 118-120° (from toluene-b.p. 80-100° light petroleum), ν_{max} 3380 (NH) and 1720 (CO) cm^{-1}, δ($CDCl_3$) 8.66 (2H, δ, J5Hz, H-4 and H-6), 7.50-7.10 (5H, m, ArH), 7.12 (1H, t, J5Hz, H-5), 6.55 (1H, d, J8Hz, NH), 6.04 (1H, d, J8Hz, benzylic CH), 4.10 (2H, q, J7Hz, CH_2) and 1.22 (3H, t, J7Hz, CH_3).

Found: C, 65.1; H, 6.0; N, 16.6%; M^+, 257.
$C_{14}H_{15}N_3O_2$ requires: C, 65.3; H, 5.9; N, 16.3%; M, 257.

(ii) The reaction mixture from the amine (371a) (0.43 g) was filtered to remove triethylamine hydrochloride and the filtrate was evaporated. The resulting red oil was treated with water (5.0 ml) and extracted with methylene chloride to yield a yellow oil (0.52 g) which was triturated with ether to give the urea (427a), (0.04 g; 18%) which formed colourless needles, m.p. 258-260° (from ethanol-dimethylformamide), ν_{max} 3300 (NH) and 1630 (CO) cm^{-1}.

Found: C, 72.2; H, 5.9; N, 18.7%; M^+, 452.
$C_{27}H_{28}N_6O$ requires; C, 71.7; H, 6.2; N, 18.6%; M^+, 452.

Evaporation of the ethereal mother liquor afforded ethyl N-[α-(4,6-dimethylpyrimid-2-yl)benzyl]carbamate (425a), (0.30 g; 53%) which formed irregular colourless crystals, m.p. 72-76° (from b.p. 80-100° light petroleum), ν_{max} 3290 (NH) and 1720 (CO) cm^{-1}, δ($CDCl_3$) 7.50-7.40 (2H, m, ArH), 7.30-7.10 (3H, m, ArH), 6.82 (1H, s, H-5), 6.70 (1H, d, J8Hz, NH), 5.95 (1H, d, J8Hz, benzylic CH), 4.10 (2H, q, J7Hz, CH_2), 2.40 (6H, s, CH_3) and 1.22 (3H, t, J7Hz, CH_3).

Found: C, 67.2; H, 6.9; N, 14.8%; M^+, 285.

$C_{16}H_{19}N_3O_2$ requires: C, 67.4; H, 6.7; N, 14.7%; M, 285.

Method B

The above reactions were repeated as in Method A but using only one equivalent of triethylamine (0.20 g, 0.002 mol).

(i) The reaction of the amine (371c) afforded the carbamate (425c) in improved yield (77%).

(ii) The reaction of the amine (371a) afforded the carbamate (425a) in improved yield (77%) and none of the urea (427a).

The Attempted Thermal Cyclisation of Ethyl N-[α-(Pyrimid-2-yl)-benzyl]carbamate (425c)

(i) A solution of the carbamate (425c), (0.15 g, 0.002 mol) in xylene (50.0 ml) was heated under reflux for 7 h with provision for the removal of any ethanol produced. The mixture on cooling gave unchanged starting-material (425c) (0.32 g; 62%) identical (m.p. and i.r. spectrum) to an authentic sample.

The xylene mother liquor was evaporated and co-evaporated

with toluene to produce a brown oil which was shown by t.l.c. in ethyl acetate over silica to be largely starting material and therefore was not investigated further.

(ii) The carbamate (425c) (0.26 g, 0.001 mol) was heated under reduced pressure in a Kugelrohr apparatus. The solid carbamate melted at 115° to give a clear liquid which distilled at 240°/0.5mmHg to give unchanged starting-material (425c) (0.25 g; 98%) identical (m.p. and i.r. spectrum) to an authentic sample.

(iii) Heating the carbamate (425c), (0.26 g, 0.001 mol) at 250° at atmospheric pressure for 15 min gave a dark oil which was flash chromatographed in ethyl acetate over silica to give unchanged starting-material (425c) (0.23 g; 87%) identical (m.p. and i.r. spectrum) to an authentic sample.

The Reaction of Ethyl N-[α-(Pyrimid-2-yl)benzyl]carbamates with Phosphoryl Chloride

A solution of the carbamate (0.002 mol) in dry 1,2-dichloroethane (25.0 ml) was treated with phosphoryl chloride (1.53 g, 0.01 mol), the mixture was heated under reflux for 4 h and worked up as described for the individual reactions below.

(i) The reaction mixture from the carbamate (425c) (0.51 g) was evaporated, treated with 2M aqueous sodium bicarbonate and ethyl acetate and shaken vigorously. The organic layer was evaporated to give a red gum (0.45 g) which was separated by flash chromatography.

Elution with methylene chloride afforded 6-ethoxy-8-phenylimidazo[1,5-a]pyrimidine (421c), (0.13 g; 28%) which

formed orange prisms, m.p. 122-123° (from b.p. 80-100° light petroleum), $\delta(CDCl_3)$ 8.35-8.20 (2H, m, ArH), 7.93 (1H, dd, J2 and 4Hz, H-2), 7.77 (1H, dd, J4 and 7Hz, H-4), 7.50-7.20 (3H, m, ArH), 6.28 (1H, dd, J4 and 7Hz, H-3), 4.66 (2H, q, J7Hz, CH_2) and 1.50 (3H, t, J7Hz, CH_3).

Found: C, 69.7; H, 5.6; N, 17.6%; M^+, 239.
$C_{14}H_{13}N_3O$ requires: C, 70.3; H, 5.4; N, 17.6%; M, 239.

Elution with methylene chloride-ethyl acetate (1:1) provided unchanged starting-material (425c) (0.11 g; 21%) identical (m.p. and i.r. spectrum) with an authentic sample.

Further elution with methylene chloride-ethyl acetate (1:1) gave 8-phenylimidazo[1,5-a]pyrimidin-6(7H)-one (426c), (0.14 g; 34%) which formed orange-red needles, m.p. 260-262° (from toluene-b.p. 80-100° light petroleum), ν_{max} 1685 (CO) cm^{-1}, $\delta(CDCl_3)$ 8.00-7.40 (4H, m, H-2, H-4 and ArH), 7.50-7.15 (3H, m, ArH) and 6.21 (1H, dd, J4 and 7Hz, H-3).

Found: C, 68.2; H, 4.5; N, 20.1%; M^+, 211.
$C_{12}H_9N_3O$ requires: C, 67.6; H, 4.3; N, 19.9%; M, 211.

(ii) The reaction mixture from the carbamate (425a) (0.57 g) was evaporated, treated with 2M aqueous sodium carbonate and ethyl acetate and shaken vigorously. The organic layer was evaporated to give an orange gum (0.59 g) which was separated by flash chromatography.

Elution with methylene chloride afforded 2,4-dimethyl-6-ethoxy-8-phenylimidazo[1,5-a]pyrimidine (421a), (0.11 g; 21%) which formed bright orange needles, m.p. 154-155° (from b.p. 80-100° light petroleum), $\delta(CDCl_3)$ 8.28 (2H, m, ArH), 7.40-7.25 (2H, m, ArH), 7.15 (1H, m, ArH), 5.89 (1H, q, J1Hz, H-3),

4.57 (2H, q, J7Hz, CH_2), 2.61 (3H, d, J1Hz, CH_3), 2.37 (3H, s, CH_3) and 1.46 (3H, t, J7Hz, CH_3).

Found: C, 72.0; H, 6.6; N, 16.0%; M^+, 267.

$C_{16}H_{17}N_3O$ requires: C, 71.9; H, 6.4; N, 15.7%; M, 267.

Further elution with methylene chloride-ethyl acetate (1:1) gave initially unchanged starting-material (425a) (0.38 g; 67%) identical (m.p. and i.r. spectrum) to an authentic sample followed by 2,4-dimethyl-8-phenylimidazo[1,5-a]pyrimidin-6(7H)-one (426a), (0.05 g, 11%) which formed orange-red needles, m.p. 253-255° (from toluene), ν_{max} 1690 (CO) cm^{-1}, $\delta(CDCl_3)$ 7.98-7.92 (2H, m, ArH), 7.39-7.31 (2H, m, ArH), 7.16-7.12 (1H, m, ArH), 5.87 (1H, q, J1Hz, H-3), 2.61 (3H, d, J1Hz, CH_3) and 2.21 (3H, s, CH_3).

Found: C, 69.7; H, 5.6; N, 17.3%; M^+, 239.

$C_{14}H_{13}N_3O$ requires: C, 70.3; H, 5.4; N, 17.6%; M, 239.

The Attempted Dealkylation of 6-Ethoxy-8-phenylimidazo[1,5-a]-pyrimidine (421c) with Phosphoryl Chloride

A solution of the ether (421c), (0.03 g, 0.0001 mol) in dry 1,2-dichloroethane (10.0 ml) was treated with phosphoryl chloride (0.08 g, 0.0005 mol) and the mixture was heated under reflux for 4 h. The solvent was removed and the residue was treated with ethyl acetate and 2M aqueous sodium bicarbonate and shaken vigorously. After separation the organic layer was shown by t.l.c. in ethyl acetate over silica to contain only the starting ether (421c) thus demonstrating that no dealkylation occurs under these conditions.

The Reaction of 2-(α-Aminobenzyl)pyrimidines with Ethoxalyl Chloride

A solution of the amine (0.002 mol) in dry dioxane (10.0 ml) was stirred and treated with triethylamine (0.20 g, 0.002 mol) followed by ethoxalyl chloride (0.27 g, 0.002 mol), the mixture was stirred at room temperature for 1 h, and worked up as described for the individual reactions below.

(i) The reaction mixture from the amine (371c) (0.37 g) was filtered to remove triethylamine hydrochloride and the filtrate was evaporated to give an amber oil which was crystallised to yield ethyl N-[α-(pyrimid-2-yl)benzyl]oxamate (431c), (0.56 g; 98%) which formed colourless crystals, m.p. 101-103° (from ethanol-light petroleum), ν_{max} 3380 (NH) and 1745 and 1690 (CO) cm^{-1}, δ($CDCl_3$) 8.90 (1H, d, J8Hz, NH), 8.72 (2H, d, J5Hz, H-4 and H-6), 7.50-7.10 (6H, m, H-5 and ArH), 6.26 (1H, d, J8Hz, benzylic CH), 4.35 (2H, q, J7Hz, CH_2) and 1.36 (3H, t, J7Hz, CH_3).

Found: C, 62.5; H, 5.1; N, 15.0%; M^+, 285.

$C_{15}H_{15}N_3O_3$ requires: C, 63.2; H, 5.3; N, 14.7%; M, 285.

(ii) The reaction mixture from the amine (371b) (0.40 g) was filtered to remove triethylamine hydrochloride and the filtrate was evaporated to give an amber oil which was crystallised to give ethyl N-[α-(4-methylpyrimid-2-yl)benzyl]oxamate (431b), (0.59 g, 98%) which formed fawn irregular crystals, m.p. 81-82° (from ethanol-light petroleum) ν_{max} 3360 (NH) and 1750 and 1700 (CO) cm^{-1}, δ($CDCl_3$) 8.93 (1H, d, J8Hz, NH), 8.49 (1H, d, J5Hz, H-6), 7.40-7.15 (5H, m, ArH), 6.99 (1H, d, J5Hz, H-5), 6.17 (1H, d, J8Hz, benzylic CH), 4.30 (2H, q, J7Hz, CH_2), 2.47 (3H, s, CH_3) and 1.32 (3H, t, J7Hz, CH_3).

Found: C, 63.7; H, 5.7; N, 14.0%; M^+, 299.

$C_{16}H_{17}N_3O_3$ requires: C, 64.2; H, 5.7; N, 14.0%; M, 299.

(iii) The reaction mixture from the amine (371a) (0.43 g) was filtered to remove triethylamine hydrochloride and the filtrate was evaporated to give an amber oil which was crystallised to give ethyl N-[α-(4,6-dimethylpyrimid-2-yl)benzyl]-oxamate (431a) (0.62 g; 99%) which formed fawn irregular crystals, m.p. 97-98° (from ethanol-light petroleum), ν_{max} 3340 (NH) and 1755 and 1700 (CO) cm^{-1}, δ($CDCl_3$) 9.01 (1H, d, J8Hz, NH), 7.45-7.35 (2H, m, ArH), 7.30-7.15 (3H, m, ArH), 6.86 (1H, s, H-5), 6.15 (1H, d, J8Hz, benzylic CH), 4.30 (2H, q, J7Hz, CH_2), 2.42 (6H, s, CH_3) and 1.33 (3H, t, J7Hz, CH_3).

Found: M^+, 313.14303 .

$C_{17}H_{19}N_3O_3$ requires: M, 313.14263 .

The Reaction of Ethyl N-[α-(pyrimid-2-yl)benzyl]oxamates with Phosphoryl Chloride

A solution of the oxamate (0.002 mol) in dry 1,2-dichloroethane (50.0 ml) was treated with phosphoryl chloride and the mixture was heated under reflux for 72 h. The mixture was evaporated, treated with ethyl acetate and 2M aqueous sodium bicarbonate and shaken vigorously. The organic phase was separated and evaporated and the product isolated as described for the individual reactions below.

(i) The organic phase obtained from reaction of the oxamate (431c) (0.57 g) was evaporated to give a brown gum (0.54 g) which was flash chromatographed in cyclohexane-ethyl acetate (1:1) to afford 6-ethoxycarbonyl-8-phenylimidazo[1,5-a]pyrimidine (432c), (0.30 g; 56%) which formed bright yellow rectangular

plates, m.p. 145-148° (from toluene-b.p. 80-100° light petroleum), ν_{max} 1690 cm^{-1}, $\delta(CDCl_3)$ 9.53 (1H, dd, J2 and 7Hz, H-4), 8.55-8.40 (2H, m, ArH), 8.45 (1H, dd, J2 and 4Hz, H-2), 7.60-7.25 (3H, m, ArH), 6.93 (1H, dd, J4 and 7Hz, H-3), 4.47 (2H, q, J7Hz, CH_2) and 1.49 (3H, t, J7Hz, CH_3).

Found: C, 66.8; H, 4.8; N, 15.4%; M^+, 267.
$C_{15}H_{13}N_3O_2$ requires: C, 67.4; H, 4.9; N, 15.7%; M, 267.

(ii) The organic phase obtained from reaction of the oxamate (431b) (0.60 g) was evaporated to give a brown gum which was purified by flash chromatography in methylene chloride over silica to give an inseparable 2:1 mixture of 6-ethoxycarbonyl-2-methyl-8-phenylimidazo[1,5-a]pyrimidine (432b) and 6-ethoxycarbonyl-4-methyl-8-phenylimidazo[1,5-a]pyrimidine (432d), (0.16 g; 82%) which formed yellow needles, m.p. 111-113° (from b.p. 80-100° light petroleum), ν_{max} 1705 cm^{-1}, $\delta(CDCl_3)$ (i) 2-methyl isomer: 9.36 (1H, d, J7Hz, H-4), 8.55-8.40 (2H, m, ArH), 7.60-7.30 (3H, m, ArH), 6.75 (1H, d, J7Hz, H-3), 4.53 (2H, q, J7Hz, CH_2), 2.63 (3H, s, CH_3) and 1.48 (3H, t, J7Hz, CH_3) and (ii) 4-methyl isomer 8.31 (1H, d, J4Hz, H-2), 8.55-8.40 (2H, m, ArH), 7.60-7.30 (3H, m, ArH), 6.63 (1H, dq, J1 and 4Hz, H-3), 4.53 (2H, q, J7Hz, CH_2), 2.77 (3H, d, J1Hz, CH_3) and 1.48 (3H, t, J7Hz, CH_3).

Found: M^+, 281.11700 .
$C_{16}H_{15}N_3O_2$ requires: M, 281.11642 .

(iii) The organic phase obtained from reaction of the oxamate (431a) (0.63 g) was evaporated to afford 2,4-dimethyl-6-ethoxycarbonyl-8-phenylimidazo[1,5-a]pyrimidine (432a), (0.42 g; 71%) which formed yellow needles, m.p. 123-125° (from toluene-

b.p. 80-100° light petroleum), ν_{max} 1710 (CO) cm^{-1}, $\delta(CDCl_3)$ 7.30-7.20 (2H, m, ArH), 6.70-6.40 (3H, m, ArH), 5.97 (1H, q, J1Hz, H-3), 4.61 (2H, q, J5Hz, CH_2), 3.45 (3H, d, J1Hz, CH_3), 3.34 (3H, s, CH_3) and 2.61 (3H, t, J5Hz, CH_3).

Found: C, 68.5; H, 5.5; N, 14.6%; M^+, 295.

$C_{17}H_{17}N_3O_2$ requires: C, 69.1; H, 5.8; N, 14.2%; M, 295.

Work-up of the aqueous mother liquor gave no further material.

The Attempted Thermal Cyclisation of Ethyl N-[α-(pyrimid-2-yl)benzyl]oxamate (431c)

(i) A solution of the oxamate (431c), (0.29 g, 0.001 mol) in dry xylene (25.0 ml) was heated under reflux for 6 h with provision for the removal by distillation of any ethanol formed. As the solvent slowly distilled fresh xylene was added to the mixture to maintain the total volume in the range 15.0-25.0 ml. Removal of the solvent gave unchanged starting-material (431c) (0.25 g; 87%) identical (m.p. and i.r. spectrum) to an authentic sample.

(ii) A solution of the oxamate (431c), (0.29 g, 0.001 mol) in dibenzyl ether (3.0 ml) was heated under reflux for 1 h. Removal of the dibenzyl ether by flash chromatography in ethyl acetate over silica gave only unchanged starting-material (431c) (0.16 g; 56%) identical (m.p. and i.r. spectrum) to an authentic sample.

8-Phenylimidazo[1,5-a]pyrimidine-6-carboxylic Acid (435c)

A solution of the ester (432c), (0.53 g, 0.002 mol) in

ethanol (10.0 ml) was treated with 2M aqueous sodium hydroxide (2.5 ml, 0.005 mol) and the mixture was heated under reflux for 15 min during which time a yellow solid was deposited. The mixture was evaporated, treated with ethyl acetate and 2M aqueous hydrochloric acid and shaken thoroughly. Filtration of the resulting three-phase system afforded 8-phenylimidazo-[1,5-a]pyrimidine-6-carboxylic acid (435c), (0.47 g; 97%) which formed yellow needles, m.p. 142-143° (from ethanol-b.p. 80-100° light petroleum), ν_{max} 1690 cm^{-1}, $\delta(CDCl_3)$ 9.00-6.75 (1H, bs, COOH), 9.54 (1H, dd, J2 and 7Hz, H-4), 8.57 (1H, dd, J2 and 4Hz, H-2), 8.50-8.30 (2H, m, ArH), 7.60-7.30 (3H, m, ArH), and 7.15 (1H, dd, J4 and 7Hz, H-3).

Found: M^+, 239.06895 .
$C_{13}H_9N_3O_2$ requires: M, 239.06947 .

The Reaction of 2-(α-Aminobenzyl)pyrimidine (371c) with Oxalyl Chloride

(i) A solution of the amine (371c), (0.56 g, 0.003 mol) in dry dioxane (15.0 ml) was stirred and treated with triethylamine (0.30 g, 0.003 mol) then oxalyl chloride (0.38 g, 0.003 mol) and the mixture was stirred at room temperature for 1 h during which time the solution turned bright red. Filtration of the mixture removed a fawn solid (0.64 g) which was treated with water to afford N,N'-di-[α-(pyrimid-2-yl)benzyl]oxamide (437c), (0.23 g; 36%) which formed colourless rectangular plates, m.p. 281-283° (from ethanol-dimethylformamide-dimethylsulphoxide), ν_{max} 3370 (NH) and 1670 (CO) cm^{-1}, $\delta[(CD_3)_2SO]$ 9.27 (2H, d, J7.5Hz, NH), 8.83 (4H, d, J5Hz, H-4 and H-6), 7.46 (2H, t, J5Hz, H-5),

7.30-7.20 (10H, m, ArH) and 6.10 (2H, d, J7.5Hz, benzylic CH).

Found: C, 67.6; H, 4.9; N, 19.9%; M^+, 424.

$C_{24}H_{20}N_6O_2$ requires: C, 67.9: H, 4.7; N, 19.8%; M, 424.

The dioxane mother liquor was evaporated to give a red foam which was triturated with ether to yield a small amount of 6,7-dihydro-6,7-dioxo-9-phenyl-8H-pyrazino[1,2-a]pyrimidine (434c), (0.06 g; 8%) which formed bright red needles, m.p. 262-264° (from toluene-ethanol-dimethylformamide), ν_{max} 3200-3100 (NH) and 1700 and 1650 (CO) cm^{-1}, $\delta[(CD)_3SO]$ 12.80-11.80 (1H, bs, NH), 8.23 (1H, dd, J2 and 8Hz, H-4), 7.86 (1H, dd, J2 and 3Hz, H-2), 7.70-7.35 (5H, m, ArH) and 6.43 (1H, dd, J3 and 8Hz, H-3).

Found: C, 64.8; H, 3.9; N, 17.7%; M^+, 239.

$C_{13}H_9N_3O_2$ requires: C, 65.3; H, 3.8; N, 17.6%; M, 239.

Evaporation of the ethereal mother liquor gave a red-brown solid residue (0.30 g) whose t.l.c. in ethyl acetate over silica showed it to be an inseparable multicomponent mixture which was not further investigated.

(ii) Repetition of the reaction as described in (i) but using two equivalents of triethylamine increased the yield of the oxamide (437c) to 65% but reduced that of the cyclised product (434c) to just 3%.

(iii) Repetition of the reaction as described in (i) but using four equivalents of triethylamine resulted in the formation of the oxamide (437c) in reduced yield (35%) with no formation of the cyclised product (434c).

The Reaction of 2-(α-Aminobenzyl)-4,6-dimethylpyrimidine (371a) with Oxalyl Chloride

A solution of the amine (371a), (0.64 g, 0.003 mol) in dry dioxane (15.0 ml) was stirred and treated with triethylamine (0.303 g, 0.003 mol) then oxalyl chloride (0.38 g, 0.003 mol) and the mixture was stirred at room temperature for 1 h during which time the solution turned bright red. Filtration of the mixture removed a fawn solid (1.1 g) which was treated with water to afford N,N'-di-[α-(4,6-dimethylpyrimid-2-yl)benzyl]-oxamide (437a), (0.31 g; 44%) which formed colourless crystals, m.p. 257-260° (from ethanol-dimethylformamide), ν_{max} 3360 (NH) and 1680 (CO) cm^{-1}, δ[$(CD_3)_2SO$] 9.29 (2H, d, J7Hz, NH), 7.39 (10H, s. ArH), 7.28 (2H, s, H-5), 6.03 (2H, d, J7Hz, benzylic CH) and 2.50 (12H, s, CH_3).

Found: C, 69.6; H, 5.8; N, 17.7%; M^+, 480.
$C_{28}H_{28}N_6O_2$ requires: C, 70.0; H, 5.8; N, 17.5%; M, 480.

The dioxane mother liquor was evaporated to give a red gum (0.34 g) whose t.l.c. in ethyl acetate over silica showed it to be a five-component mixture. Flash chromatography of the gum in ethyl acetate over silica gave an orange gum (0.19 g) which was triturated with ether to afford 6,7-dihydro-6,7-dioxo-2,4-dimethyl-9-phenyl-8H-pyrazino[1,2-a]pyrimidine (434a) (0.07 g; 9%) which formed bright orange needles, m.p. 212-215° (from ethanol-b.p. 80-100° light petroleum), ν_{max} 3140 (NH) and 1740 and 1650 (CO) cm^{-1}, δ($CDCl_3$) 9.90-9.50 (1H, bs, NH), 7.70-7.55 (2H, m, ArH), 7.30-7.10 (3H, m, ArH), 5.82 (1H, q, J1Hz, H-3) 2.69 (3H, d, J1Hz, CH_3) and 2.16 (3H, s, CH_3).

Found: C, 66.8; H, 4.8; N, 15.7%; M^+, 267.

$C_{15}H_{13}N_3O_2$ requires: C, 67.4; H, 4.9; N, 15.7%; M, 267.

Evaporation of the ethereal liquor gave a gum which was not further investigated.

The Reaction of 2-(α-Aminobenzyl)-6-methylpyrimidin-4(3H)-one (372) with Oxalyl Chloride

A solution of the amine (372), (0.43 g, 0.002 mol) in dry dioxane (10.0 ml) was treated sequentially with triethylamine (0.20 g, 0.002 mol) and oxalyl chloride (0.25 g, 0.002 mol) and the mixture was stirred at room temperature for 1 h, the initially colourless solution turning bright yellow during this time. The mixture was filtered to remove triethylamine hydrochloride and the filtrate was evaporated to afford an orange glass (0.59 g) which was triturated with ether to yield the oxamide (441), (0.33 g; 69%) which formed colourless crystals, m.p. 235-240° (from dimethylformamide), ν_{max} 3370 (NH) and 1700 and 1660 (CO) cm^{-1}.

Found: M^+, 484.16749 .

$C_{26}H_{24}N_6O_4$ requires: M, 484.16589 .

Evaporation of the ethereal mother liquor gave a yellow gum (0.18 g) which was shown by t.l.c. in ethyl acetate over silica to be a multicomponent mixture which was not further investigated.

8-Phenyl-6-(8-phenylimidazo[1,5-a]pyrimid-6-yl)imidazo[1,5-a]-pyrimidine

A solution of N,N'-di-[α-(pyrimid-2-yl)benzyl]oxamide (437c), (0.42 g, 0.001 mol) in dry 1,2-dichloroethane (20.0 ml) was treated with phosphoryl chloride (1.53 g, 0.01 mol) and the mixture was heated under reflux for 18 h. The solvent was removed and the residue was treated with ethyl acetate and 2M aqueous sodium bicarbonate. After shaking the three-phase system was filtered to afford the imidazopyrimidylimidazo-pyrimidine (438c), (0.35 g; 89%) which formed orange needles m.p. >360° (from dimethylformamide).

Found: M^+, 388.14371 .

$C_{24}H_{16}N_6$ requires: M, 388.14364 .

Separation and evaporation of the ethyl acetate layer gave only a small amount of yellow gum (0.03 g) which was not further investigated.

2-(α-Chloroacetamidobenzyl)pyrimidine (445)

A solution of the amine (371c), (0.56 g, 0.003 mol) in dry dioxane (15.0 ml) was stirred and treated with triethylamine (0.30 g, 0.003 mol) followed by chloroacetyl chloride (0.34 g, 0.005 mol). After stirring for 1 h the mixture was filtered to remove triethylamine hydrochloride and the filtrate was evaporated to give a brown oil (1.1 g) which was flash chromatographed in methylene chloride over silica to afford 2-(α-chloroacetamidobenzyl)pyrimidine (445), (0.66 g; 85%) which formed colourless crystals, m.p. 107-110° (from toluene-b.p. 80-100° light petroleum), ν_{max} 3390 (NH) and 1670 (CO) cm^{-1},

$\delta(CDCl_3)$ 8.59 (2H, d, J5Hz, H-4 and H-6), 8.48 (1H, d, J7Hz, NH), 7.40-7.10 (5H, m, ArH), 7.05 (1H, t, J5Hz, H-5), 6.17 (1H, d, J7Hz, benzylic CH) and 2.98 (2H, s, CH_2).

Found: C, 59.4; H, 4.5; N, 16.3%; M^+, 263/261.

$C_{13}H_{12}ClN_3O$ requires: C, 59.7; H, 4.6; N, 16.1%; M, 261.5.

The Attempted Reaction of 2-(α-Chloroacetamidobenzyl)pyrimidine (445) with Phosphoryl Chloride

A solution of the amide (445), (0.52 g, 0.002 mol) in dry 1,2-dichloroethane (50.0 ml) was treated with phosphoryl chloride (1.53 g, 0.01 mol) and the mixture was heated under reflux for 5 h. The solvent was removed and the residue was treated with ethyl acetate and 2M aqueous sodium bicarbonate. After thorough mixing the separated organic layer was evaporated to give a yellow gum (0.21 g) which was shown by t.l.c. in methylene chloride-ethyl acetate (1:1) over silica to be a complex multi-component mixture which was not further investigated.

The Preparation of N-[α-(Pyrimid-2-yl)benzyl]-2,5-anhydro-3,4,6-tri-O-benzoyl -D-allonamides

A solution of the amine (0.002 mol) in dry methylene chloride (20.0 ml) was stirred and treated with 2,5-anhydro-3,4,6-tri-O-benzoyl -D-allonic acid (451) (0.96 g, 0.002 mol) in one portion. A solution of N,N'-dicyclohexylcarbodiimide (0.45 g, 0.002 mol) in dry methylene chloride (1.0 ml) was added dropwise and the mixture was stirred at room temperature for 2 h and worked up as described for the individual reactions below.

(i) The reaction mixture from the amine (371c) (0.37 g) was filtered to remove N,N'-dicyclohexylurea and the filtrate was evaporated to give a yellow foam which was purified by flash chromatography in cyclohexane-ethyl acetate (4:1) over silica to yield a 1:1 mixture of the C-1 epimers of N-[α-(pyrimid-2-yl)benzyl]-2,5-anhydro-3,4,6-tri-O-benzoyl -D-allonamide (452c), (1.10 g; 84%) as a colourless foam, ν_{max} 3400-3200 (NH) and 1720 and 1680 (CO) cm^{-1} $\delta(CDCl_3)$ 8.70-8.50 (3H, m, H-4, H-6 and NH), 8.10-7.90 (6H, m, ArH), 7.60-7.20 (14H, m, ArH), 7.16 and 7.05 (1H, t, H-5), 6.30-6.20 (1H, d, benzylic CH), 6.15-5.80 (2H, m, H-2' and H-3') and 5.00-4.60 (4H, m, H-1', H-4' and H-5').

Found: C, 69.2; H, 4.7; N, 6.1%; M^+, 657.
$C_{38}H_{31}N_3O_8$ requires: C, 69.4; H, 4.7; N, 6.4%; M, 657.

(ii) The reaction mixture from the amine (371b) (0.40 g) was filtered to remove N,N'-dicyclohexylurea and the filtrate was evaporated to give a brown gum which was purified by flash chromatography in cyclohexane-ethyl acetate (4:1) over silica to yield a 1:1 mixture of diastereoisomers of N-[α-(4-methyl-pyrimid-2-yl)benzyl]-2,5-anhydro-3,4,6-tri-O-benzoyl -D-allonamide (452b), (2.29 g; 100%) as a colourless foam, ν_{max} 3400-3300 (NH) and 1725 and 1680 (CO) cm^{-1}, $\delta(CDCl_3)$ 8.70 (1H, d, NH), 8.48 and 8.35 (1H, d, H-6), 8.10-7.90 (6H, m, ArH), 7.60-7.10 (14H, m, ArH), 7.00 and 6.90 (1H, d, H-5), 6.18 (1H, d, benzylic CH), 6.10-5.80 (2H, m, H-2' and H-3'), 5.00-4.60 (4H, m, H-1', H-4' and H-5') and 2.48 and 2.44 (3H, s, CH_3).

Found: C, 69.6; H, 5.1; N, 6.5%; M^+, 671.
$C_{39}H_{33}N_3O_8$ requires: C, 69.7; H, 5.0; N, 6.3%; M, 671.

(iii) The reaction mixture from the amine (371a) (0.43 g) was filtered to remove N,N'-dicyclohexylurea and the filtrate was evaporated to give an orange gum which was purified by flash chromatography in cyclohexane-ethyl acetate (4:1) over silica to yield a 1:1 mixture of diastereoisomers of N-[α-(4,6-dimethylpyrimid-2-yl)benzyl]-2,5-anhydro-3,4,6-tri-O-benzoyl -D-allonamide (452a), (1.28 g, 93%) as a colourless foam, ν_{max} 3400-3300 (NH) and 1725 and 1685 (CO) cm^{-1}, δ($CDCl_3$) 8.75 (1H, d, NH), 8.10-7.80 (6H, m, ArH), 7.60-7.10 (14H, m, ArH), 6.84 and 6.70 (1H, s, H-5), 6.15 and 6.10 (1H, d, benzylic CH), 6.10-5.80 (2H, t, H-2' and H-3'), 4.90-4.70 (4H, m, H-1' H-4' and H-5') and 2.4 (6H, s, CH_3).

Found: C, 69.8; H, 5.3; N, 5.9%; M^+, 685.
$C_{40}H_{35}N_3O_8$ requires: C, 70.1; H, 5.1; N, 6.1%; M, 685.

(iv) The reaction mixture from the amine (372) (0.43 g, 0.002 mol) was filtered to remove N,N'-dicyclohexylurea and the filtrate was evaporated to give a pale yellow foam which was purified by flash chromatography in cyclohexane-ethyl acetate (3:1) over silica to yield a 1:1 mixture of diastereoisomers of 2-[α-(2,5-anhydro-3,4,6-tri-O-benzoyl -D-allonamido)benzyl]--6-methylpyrimidin-4(3H)-one (461), (1.08 g; 79%) as a colourless foam, ν_{max} 3380 (NH) and 1730 and 1670 (CO) cm^{-1} δ($CDCl_3$) 8.48 and 8.38 (1H, d, NH), 8.10-7.80 (6H, m, ArH), 7.60-7.20 (14H, m, ArH), 6.10 (2H, m, H-5 and H-2'), 5.95-5.70 (2H, m, H-3' and benzylic CH), 4.87 (1H, d, H-1'), 4.85-4.60 (3H, m, H-4' and H-5') and 1.30 and 1.28 (3H, s, CH_3).

Found: M^+, 687.22839 .
$C_{39}H_{33}N_3O_9$ requires: M, 687.22166 .

The Preparation of 6-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-imidazo[1,5-a]pyrimidines

A solution of the amide (0.001 mol) in dry 1,2-dichloroethane (100 ml) was treated with phosphoryl chloride (0.76 g, 0.005 mol) and the mixture was heated under reflux for 6 h, adding pyridine (0.5 ml) after 5 h to neutralise the HCl produced. The solvent was removed and the residue was treated with ethyl acetate and 2M aqueous sodium bicarbonate and shaken vigorously. The organic phase was separated and the products isolated as described for the individual reactions below.

(i) The organic layer obtained from the reaction of the amide (452c) (0.66 g) was evaporated to give a yellow gum (0.76 g) which was flash chromatographed in cyclohexane-ethyl acetate (3:1) over silica to give as the initial fraction 8-phenyl-6-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)imidazo[1,5-a]pyrimidine (453c; R^3=Bz), (0.33 g; 50%) as a yellow foam, ν_{max} 1720 (CO) cm^{-1}; δ($CDCl_3$) 8.40-8.35 (3H, m, H-4 and ArH), 8.12 (1H, dd, H-2), 8.07 (2H, m, ArH), 7.97 (2H, m, ArH), 7.80 (2H, m, ArH), 7.70-7.20 (12H, m, ArH), 6.68 (1H, dd, H-3), 6.45 (1H, m, H-2'), 6.20 (1H, t, H-3'), 5.79 (1H, d, H-1') and 4.95-4.55 (3H, m, H-4' and H-5').

Found: C, 69.2; H, 4.7; N, 6.4%; M^+, 639.
$C_{38}H_{29}N_3O_7$ requires: C, 69.4; H, 4.7; N, 6.1; M, 639.

However the ^1H n.m.r. spectrum showed that the desired β-anomer was contaminated with about 30% of the isomeric α-anomer (454c; R^3=Bz) in particular the α-anomer 1' proton showing as a doublet at δ6.14.

Further elution gave a colourless foam which was shown

to be unchanged starting-material (452c) (0.27 g; 41%) identical (^{1}H n.m.r. spectrum) to an authentic sample.

(ii) The organic layer obtained from the reaction of the amide (452b) (0.67 g) was evaporated to give a yellow foam (0.70 g) which was flash chromatographed in cyclohexane-ethyl acetate (4:1) to give as the first fraction an orange gum (0.05 g; 17%) whose n.m.r. spectrum was identical to that of the previously synthesised 2:1 mixture of the isomers 6,8-diphenyl-2-methylimidazo[1,5-a]pyrimidine (404b) and 6,8-diphenyl-4-methylimidazo[1,5-a]pyrimidine (404d).

Further elution gave 2-methyl-8-phenyl-6-(2,3,5-tri-O-benzoyl-β-D-ribofuranosylimidazo[1,5-a]pyrimidine (453b; R^3=Bz), (1.10 g; 59%) as a yellow foam, ν_{max} 1725 (CO) cm^{-1}, δ($CDCl_3$) 8.50-7.70 (9H, m, H-4 and ArH), 7.70-7.10 (12H, m, ArH), 7.05-6.95 (1H, m, H-2'), 6.70-6.00 (2H, m, H-3 and H-3'), 5.86 (1H, d, H-1'), 4.90-4.40 (3H, m, H-4' and H-5') and 3.84 (3H, s, CH_3).

Found: C, 71.5; H, 4.8; N, 6.2%; M^+, 653.
$C_{39}H_{31}N_3O_7$ requires: C, 71.7; H, 4.8; N, 6.4%; M, 653.

However the ^{1}H n.m.r. spectrum showed that the 2-methyl compound (453b; R^3=Bz) was contaminated with about 30% of an isomeric compound, probably the 4-methyl isomer (453d; R^3=Bz).

Further elution provided a third fraction as unchanged starting-material (452b) (0.14 g; 21%) identical (^{1}H n.m.r. spectrum) to an authentic sample.

(iii) The organic layer obtained from the reaction of the amide (452a) (0.69 g) was evaporated to give a yellow foam (0.66 g) which was flash chromatographed in cyclohexane ethyl acetate (5:1) over silica to give as the first fraction 2,4-dimethyl-8-phenyl-6-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)imidazo[1,5-a]-

pyrimidine (453a; R^3=Bz), (0.15 g; 23%) as a yellow foam, ν_{max} 1730 (CO) cm^{-1}, $\delta(CDCl_3)$ 8.50 (2H, m, ArH), 8.08 (2H, m, ArH), 7.98 (2H, m, ArH), 7.88 (2H, m, ArH) 7.60-7.20 (11H, m, ArH), 7.05 (1H, m, ArH), 6.96 (1H, dd, J3 and 5Hz, H-2'), 6.42 (1H, dd, J5 and 7Hz, H-3'), 6.30 (1H, s, H-5), 5.83 (1H, d, J3Hz, H-1'), 4.80 (1H, dt, J3 and 7Hz, H-4'), 4.70 (1H, dd, J3 and 12Hz, H-5'), 4.42 (1H, dd, J3 and 12Hz, H-5'), 2.88 (3H, s, CH_3) and 2.50 (3H, s, CH_3).

A small amount of yellow solid obtained as the second fraction was shown to be identical (^{1}H n.m.r. spectrum) to a sample of the previously synthesised 2,4-dimethyl-6,8-diphenylimidazo[1,5-a]pyrimidine (404a), (0.02 g; 8%).

The third fraction was identified as 2,4-dimethyl-8-phenyl-6-(2,3,5-tri-O-benzoyl-α-D-ribofuranosyl)imidazo[1,5-a]pyrimidine (454a; R^3=Bz), (0.10 g; 15%) as a yellow foam, ν_{max} 1730 (CO) cm^{-1}, $\delta(CDCl_3)$ 8.26 (2H, m, ArH), 8.13 (2H, m, ArH), 7.94 (2H, m, ArH), 7.76 (2H, m, ArH), 7.65-7.10 (12H, m, ArH), 6.27 (1H, t, J5.5Hz, H-2'), 6.21 (1H, s, H-5), 6.17 (1H, d, J5.5Hz, H-1'), 6.00 (1H, t, J5.5Hz, H-3'), 5.31 (1H, dt, J3.5 and 5.5Hz, H-4'), 4.92 (1H, dd, J3.5 and 11.5Hz, H-5'), 4.70 (1H, dd, J5.5 and 11.5Hz, H-5'), 2.75 (3H, s, CH_3) and 2.48 (3H, s, CH_3).

The final fraction was shown to be starting-material (452a) (0.36 g; 53%) identical (^{1}H n.m.r. spectrum) to an authentic sample.

(iv) The organic layer obtained from the reaction of the amide (461) (0.69 g) was evaporated to give a yellow gum which was flash chromatographed in cyclohexane-ethyl acetate (1:1) to afford a yellow foam whose ^{1}H n.m.r. spectrum suggested that

it was a complex mixture of isomers (0.56 g; 69%).

Found: C, 68.2; H, 4.6; N, 5.9%; M^+, 686/688.
$C_{39}H_{30}ClN_3O_7$ requires: C, 68.1; H, 4.4; N, 6.1%; M, 686.5.

8-Phenyl-6-β-D-ribofuranosylimidazo[1,5-a]pyrimidine (453c; R^3=H).

A solution of a 70:30 mixture of the tri-O-benzoyl nucleoside diastereoisomers (453c; R^3=Bz) and (454c; R^3=Bz), (0.34 g, 0.00053 mol) in methanol (50.0 ml) was saturated with ammonia at 0°C (ice-salt bath) and the mixture was left stoppered at room temperature for 41 h. Evaporation afforded a yellow solid which was crystallised to yield the pure β-nucleoside (453c; R^3=H), (0.08 g; 46%) which formed bright yellow needles, m.p. 220-223° (from ethyl acetate-ethanol), ν_{max} 3400-3200 (OH) cm^{-1}, δ[$(CD_3)_2SO$] 8.96 (1H, d, H-4), 8.33 (3H, m, H-2 and ArH), 7.46 (2H, t, ArH), 7.27 (1H, t, ArH), 6.82 (1H, dd, H-3), 5.50-5.00 (3H, bs, OH), 5.19 (1H, d, H-1'), 4.58 (1H, t, H-2'), 4.15 (1H, t, H-3'), 3.97 (1H, q, H-4') and 3.62 (2H, dq, H-5').

Found: C, 61.9; H, 5.2; N, 12.4%; M^+, 327.
$C_{17}H_{17}N_3O_4$ requires: C, 62.4; H, 5.0; N, 12.8%; M, 327.

Evaporation of the ethyl acetate-ethanol mother liquor gave a yellow gum suggesting that it was a 3:2 mixture of 8-phenyl-6-α-D-ribofuranosylimidazo[1,5-a]pyrimidine (454c; R^3=H) and the β-nucleoside (453c; R^3=H). The gum was not further investigated.

6-Methyl-8-phenyl-6-β-D-ribofuranosylimidazo[1,5-a]pyrimidine (453b; R^3=H)

A 70:30 mixture of the tri-O-benzoyl nucleoside isomers

(453b; R^3=Bz) and (454b; R^3=Bz), (0.78 g, 0.0012 mol) was dissolved in methanol (100 ml), the solution was saturated with ammonia at 0° (ice-salt bath) and the mixture was left stoppered at room temperature for 27 h. Evaporation afforded a yellow solid which was crystallised to afford the pure nucleoside (453b; R^3=H), (0.22 g; 54%) which formed golden crystals, m.p. 234-237° (from ethanol), ν_{max} 3365-3310 (OH) cm^{-1}, δ[$(CD_3)_2SO$] 8.84 (1H, d, H-4), 8.34 (2H, d, ArH), 7.44 (2H, t, ArH), 7.24 (1H, t, ArH), 6.76 (1H, d, H-3), 5.16 (1H, d, H-1'), 4.56 (1H, t, H-2'), 4.14 (1H, t, H-3'), 3.95 (1H, q, H-4'), 3.60 (2H, dq, H-5') and 2.55 (3H, s, CH_3).

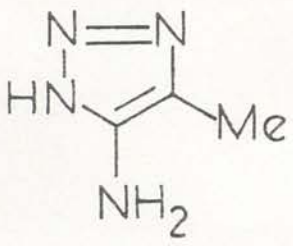
Found: C, 63.3; H, 5.6; N, 12.3%; M^+, 341.

$C_{18}H_{19}N_3O_4$ requires: C, 63.3; H, 5.6; N, 12.3%; M, 341.

Evaporation of the ethanolic mother liquor gave a yellow residue (0.11 g) which was shown by ^1H n.m.r. spectroscopy to be a complex mixture containing more of the product. The mixture was not further investigated.

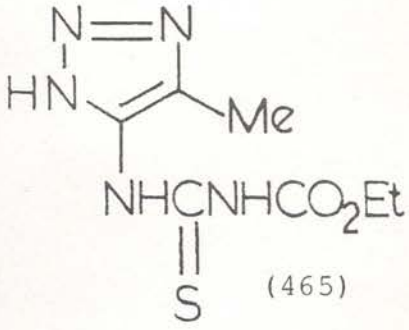
Chapter 4

Studies on the Synthesis and Reactivity of the 1,2,3-Triazolo[1,5-a]-1,3,5-triazine Ring System



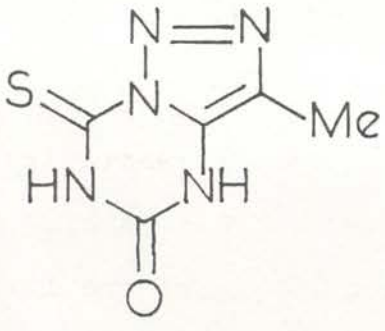
(464)

(i)

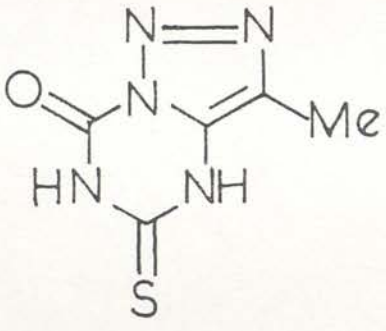


(465)

(ii)



(466)



(467)

(i) EtO_2CNCS

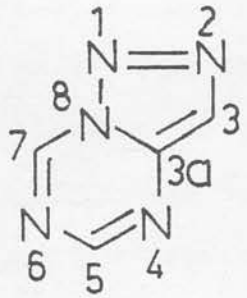
(ii) NaOH

Scheme 117

Studies on the synthesis and Reactivity of the 1,2,3-Triazolo[1,5-a]-1,3,5-triazine Ring System

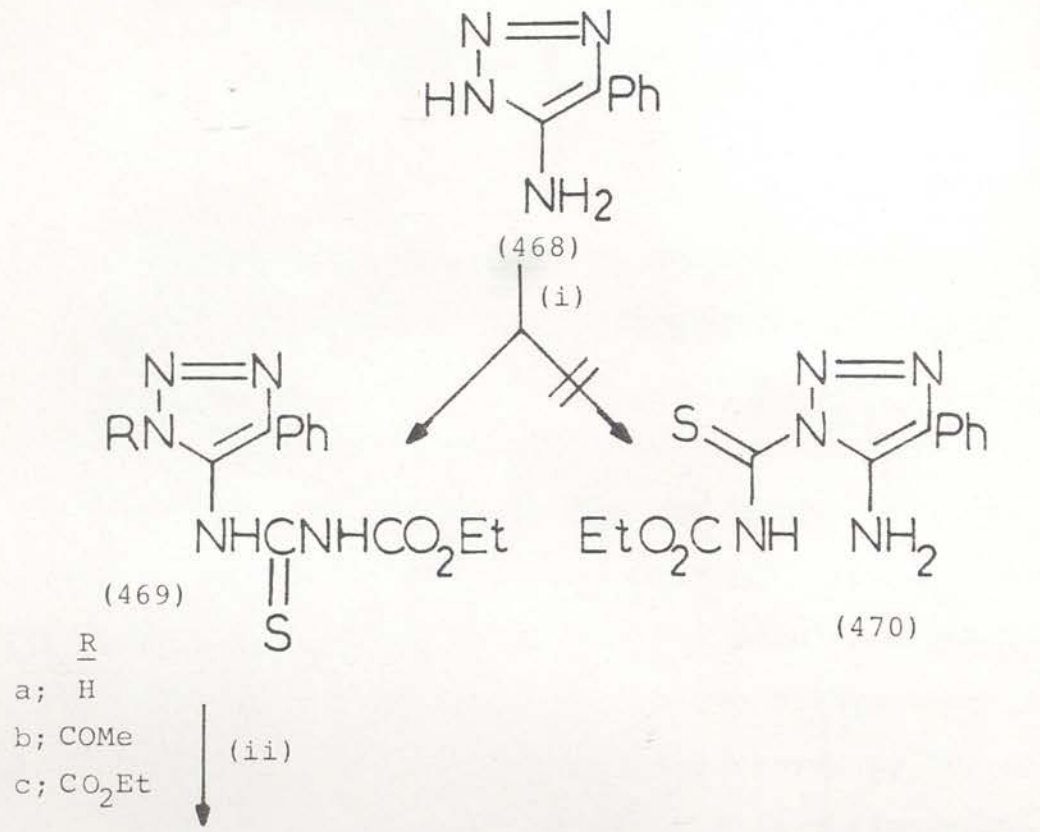
4.1 Introduction

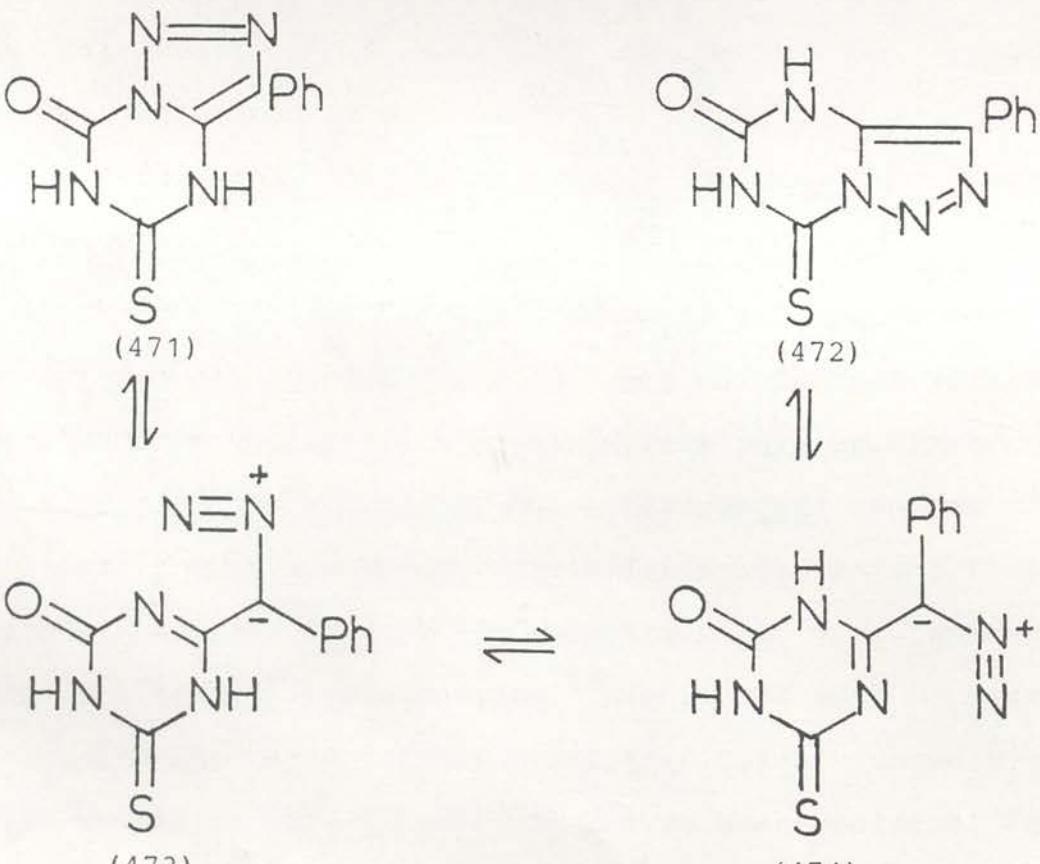
The synthetic strategy of employing bridgehead-fused 1,2,3-triazolo[1,5-a]pyrimidine derivatives as synthetic intermediates for a variety of 2-functionalised pyrimidines ultimately leading to a new synthesis of the imidazo[1,5-a]-pyrimidine ring system has been successfully demonstrated in Chapters 2 and 3. Consequently it was of interest to see if other bridgehead-fused 1,2,3-triazole ring systems could be used as heterocyclic synthetic intermediates. It was therefore decided to investigate the synthesis and reactivity of the 1,2,3-triazolo[1,5-a]-1,3,5-triazine ring system (463). This



(463)

nucleus was chosen for study not only because its reactivity might mirror that of the previously studied 1,2,3-triazolo-[1,5-a]pyrimidine ring system, being a 6-azalogue of the latter, but also because the synthesis and reactivity of the 1,2,3-triazolo[1,5-a]-1,3,5-triazine ring system has been little investigated, only one derivative having been reported in the literature. Thus Fox *et al* [67] have reported (Scheme 117) that 5-amino-4-methyl-1H-1,2,3-triazole (464) reacts with ethoxy-carbonyl isothiocyanate at the exocyclic N-atom to afford the





(i) EtO_2CNCS

(ii) NaOH

Scheme 118

disubstituted thiourea (465). Treatment of the thiourea (465) with sodium hydroxide was reported[67] to give the 7-oxo-5-thioxotriazolotriazine (467) on the basis of ^{1}H n.m.r. spectroscopy and elemental analysis. However, no evidence was presented to exclude the alternative 5-oxo-7-thioxo structure (466) derivable from the initially-formed triazolotriazine (467) by Dimroth rearrangement.[46] It was therefore of interest to re-examine this type of reaction as well as the synthesis and reactivity of 1,2,3-triazolo[1,5-a]-triazines in general.

4.2 Synthesis and Reactivity of Some 1,2,3-Triazolo[1,5-a]-1,3,5-triazines

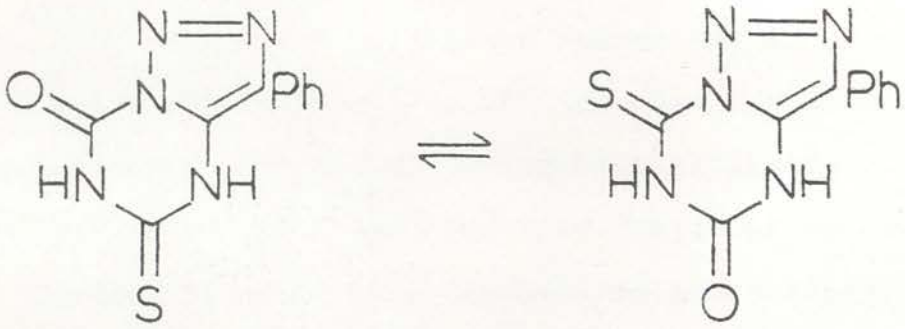
Since the 5-amino-4-phenyl-1H-1,2,3-triazole [Scheme 118; (468)] was readily available (see Chapter 2) it was decided to investigate the reaction of this compound with ethoxycarbonyl isothiocyanate. In practice the amine (468) reacted with ethoxycarbonyl isothiocyanate in 1,2-dimethoxyethane at room temperature to give a yellow product in good yield (65%) which gave analytical and spectral data consistent with the molecular formula $C_{12}H_{13}N_5O_2S$. This together with the presence of a urethane carbonyl absorption at 1725 cm^{-1} in its i.r. spectrum as well as the associated NH absorption allowed the compound to be assigned the thiourea structure (469a). This structure is also supported by the ^{1}H n.m.r. spectrum of the compound (469a) which shows an ethyl group as a three-proton triplet at δ1.23 coupled to a two-proton quartet at δ4.18 and, as well as proton signals due to a phenyl group, three broad singlets above δ9.50, attributable to three distinct NH groups. Confirmation that

the isothiocyanate had reacted at the exocyclic amino-group of the triazole (468) to give the thiourea (469a) and not at the endocyclic NH to give the isomer (470) was provided by reaction of the product with acetic anhydride. This reaction afforded a good yield of a mono-acylated compound whose i.r. spectrum contained carbonyl absorptions at 1720 and 1770 cm^{-1}. While the lower frequency absorption is attributable to the urethane grouping the higher frequency carbonyl is consistent with the presence of a ring N-acetyl and thus the product was assigned the structure (469b). Analytical data and ^1H n.m.r. spectroscopy of the product (469b) also agreed with this assignment.

When the preparation of the thiourea (469a) was repeated on a larger scale a by-product was isolated in low yield (7%) which gave analytical and mass spectral data consistent with the molecular formula $C_{15}H_{17}N_5O_4S$. The i.r. spectrum of the compound contained two ester carbonyl bands at 1730 and 1785 cm^{-1} attributable to the presence of a urethane substituent and N-ethoxycarbonyl groups respectively. On the basis of this i.r. absorption and the presence in its ^1H n.m.r. spectrum of signals due to the protons of two distinct ethyl groups, the compound is tentatively assigned the structure (469c) however the mode of formation of this by-product is not clear.

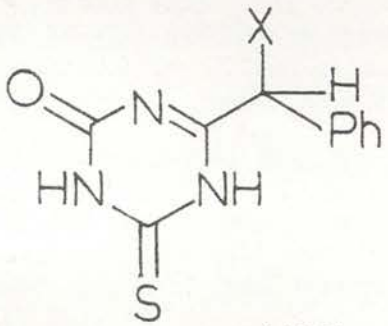
When the thiourea derivative (469a) was heated under reflux with sodium ethoxide in ethanol (Scheme 118) a product was obtained in good yield whose analytical data gave the molecular formula $C_{10}H_7N_5OS$ in accord with either of the expected triazolotriazine structures (471) and (472). However the i.r. spectrum of the solid contained a strong carbonyl absorption at 1770 cm^{-1} and a weaker carbonyl band at 1710 cm^{-1} consistent

with a mixture of both isomers (471) and (472). On the reasonable assumption that the 7-oxo structure (471) will show the higher carbonyl frequency (ring N-acyl-1,2,3-triazole structure), the carbonyl band at 1770 cm^{-1} is assigned to this isomer which therefore predominates in the mixture, the minor component being the 5-oxo isomer (472) (ν_{max} 1710 cm^{-1}). On crystallisation of the isomer mixture of (471) and (472) from ethanol the carbonyl band at 1770 cm^{-1} disappeared while that at 1710 cm^{-1} intensified indicating the thermal conversion of the 7-oxo isomer (471) entirely into the 5-oxo structure (472). This transformation can be understood in terms of Dimroth rearrangement [(471)⇌(473)⇌(474)⇌(472)] closely related examples of which have been described in the literature.[50,61,62] Heating the isomer mixture of (471) and (472) for a longer time (30 min) in ethanol resulted in the formation of a readily separated mixture of the thiourea (469a) as the minor component and as the major product a yellow gum whose mass spectrum showed a parent ion at m/e 232. This, together with the i.r. spectrum which showed NH and carbonyl absorptions at 3300 and 1700 cm^{-1} and the ^1H n.m.r. spectrum which showed proton resonances due to a single ethyl group and a single phenyl group, allowed assignment of the urethane structure (475) to the yellow gum. The formation of the thiourea (469a) and the urethane (475) by prolonged heating of the isomer mixture of (471) and (472) in ethanol can be explained (Scheme 119) by ethanolysis of the 7-oxo and 5-oxo compounds (471) and (472) respectively.



(471) (472)

(i) or (ii)



(476)

X

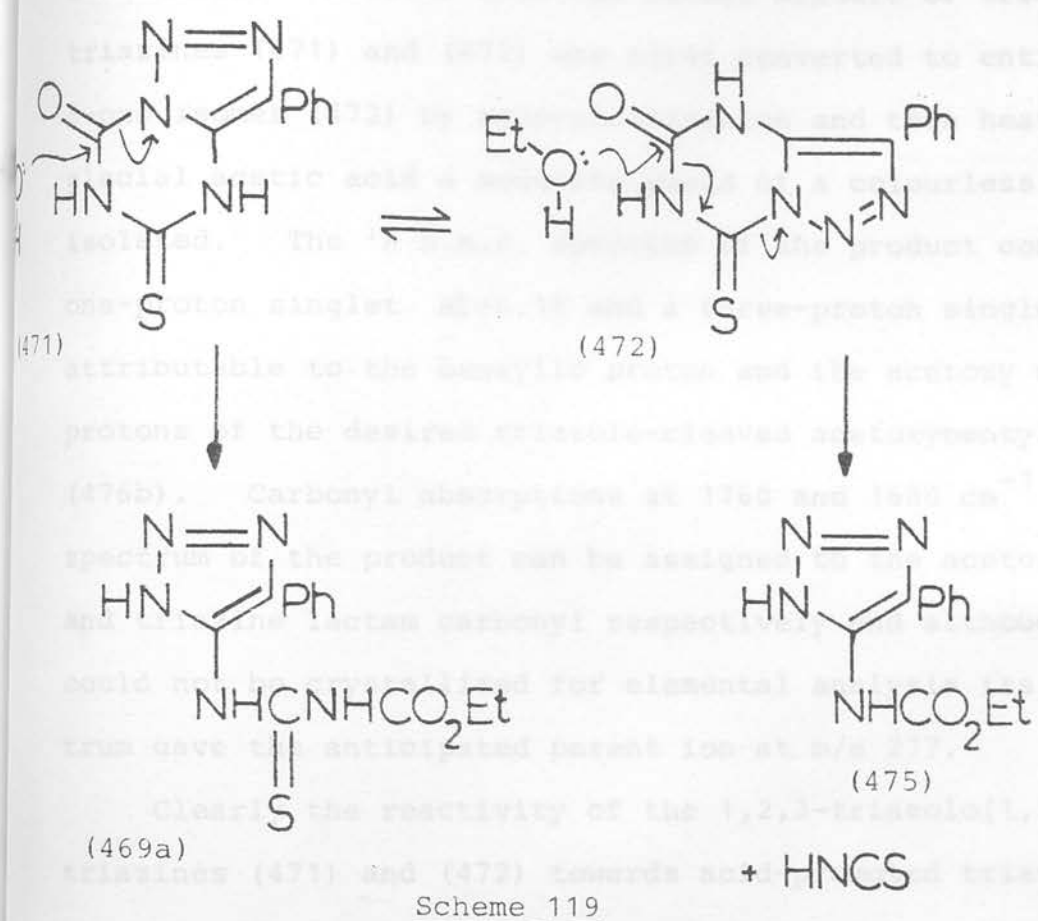
a; Cl

b; OAc

(i) AcOH

(ii) AcOH-AcCl

Scheme 120



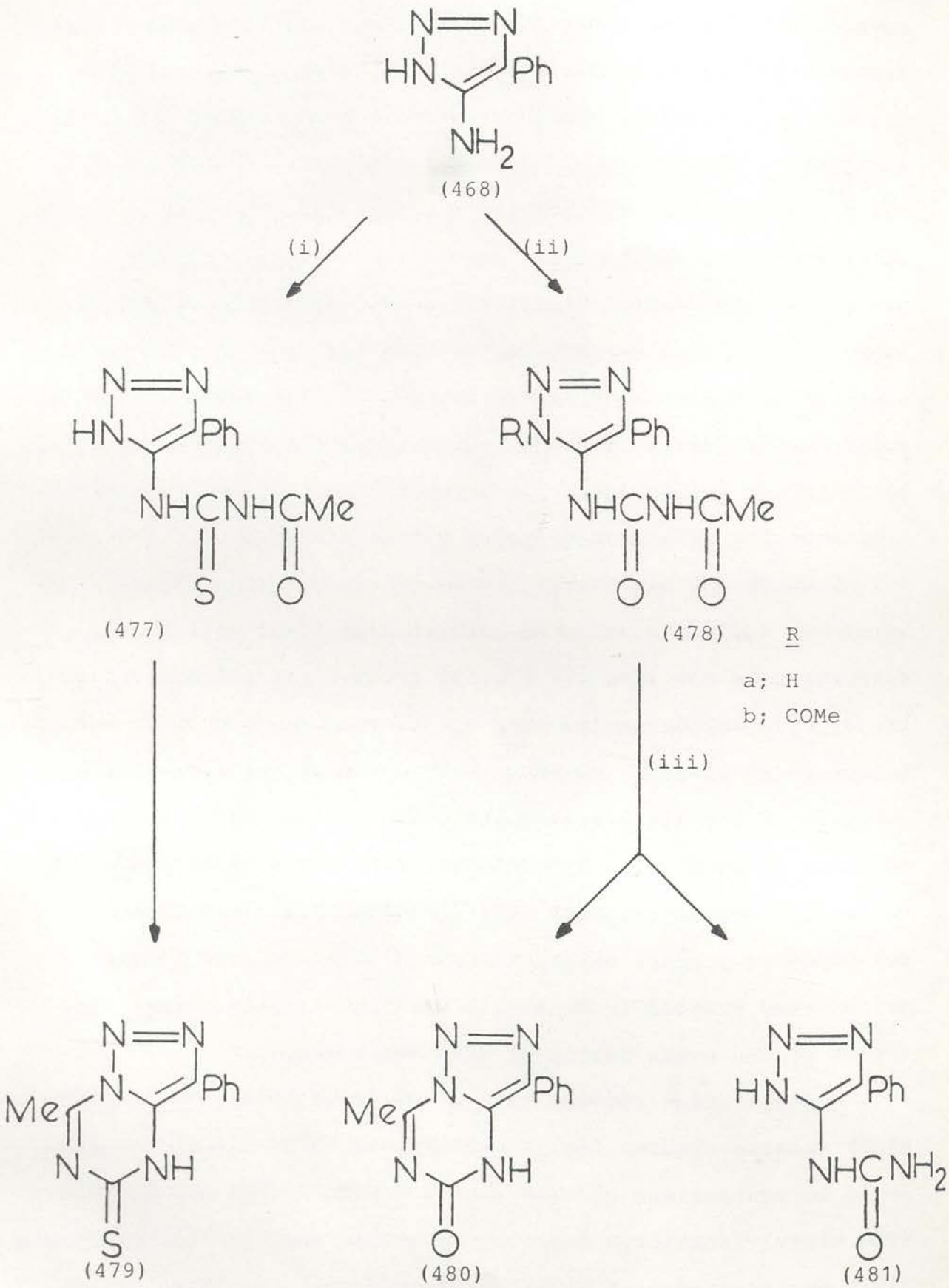
Scheme 119

When the isomer mixture of triazolotriazines (471) and 472), in which the former largely predominates, was heated in acial acetic acid (Scheme 120) with a view to preparing the iazole-cleaved acetoxy-compound (476b) only a complex mixture s obtained. Similarly heating the isomer mixture of triazolo-iazines (471) and (472) with an acetyl chloride-acetic acid xture also gave a complicated mixture from which none of the sired chlorobenzyltriazine (476a) was isolated. A possible planation for the production of complex mixtures from these tempted triazole scission reactions is the observed ease of lvolysis of the triazine ring of the triazolotriazines (471) d (472). Thus the 5- and/or 6-membered ring of the triazolo-iazines (471) and (472) may be being cleaved under these

conditions. However when the isomer mixture of triazolotriazines (471) and (472) was first converted to entirely the 5-oxo isomer (472) by recrystallisation and then heated with glacial acetic acid a moderate yield of a colourless solid was isolated. The ^{1}H n.m.r. spectrum of the product contained a one-proton singlet at δ6.18 and a three-proton singlet at δ2.15 attributable to the benzylic proton and the acetoxy methyl protons of the desired triazole-cleaved acetoxybenzyltriazine (476b). Carbonyl absorptions at 1760 and 1680 cm^{-1} in the i.r. spectrum of the product can be assigned to the acetoxy carbonyl and triazine lactam carbonyl respectively and although the solid could not be crystallized for elemental analysis its mass spectrum gave the anticipated parent ion at m/e 277.

Clearly the reactivity of the 1,2,3-triazolo[1,5-a]-1,3,5-triazines (471) and (472) towards acid-promoted triazole-ring cleavage does not parallel that of the closely related 1,2,3-triazolo[1,5-a]pyrimidine ring system (see Chapter 2). It was therefore of interest to attempt the preparation of some further examples of the 1,2,3-triazolo[1,5-a]-1,3,5-triazine ring system in order to more fully investigate the reactivity of these compounds towards triazole ring cleavage. In particular it was hoped to prepare direct 6-azalogues of those triazolopyrimidines studied in Chapter 2 and thus closely compare the effect of the 6-aza moiety on such reactivity.

A preparation (Scheme 121) of the triazolotriazine (479) might involve cyclisation of the thiourea (477) which in turn could be synthesised by reaction of the aminotriazole (468) with acetyl isothiocyanate. In practice when the aminotriazole (468) was treated with acetyl isothiocyanate the reaction was



(i) MeCONCS

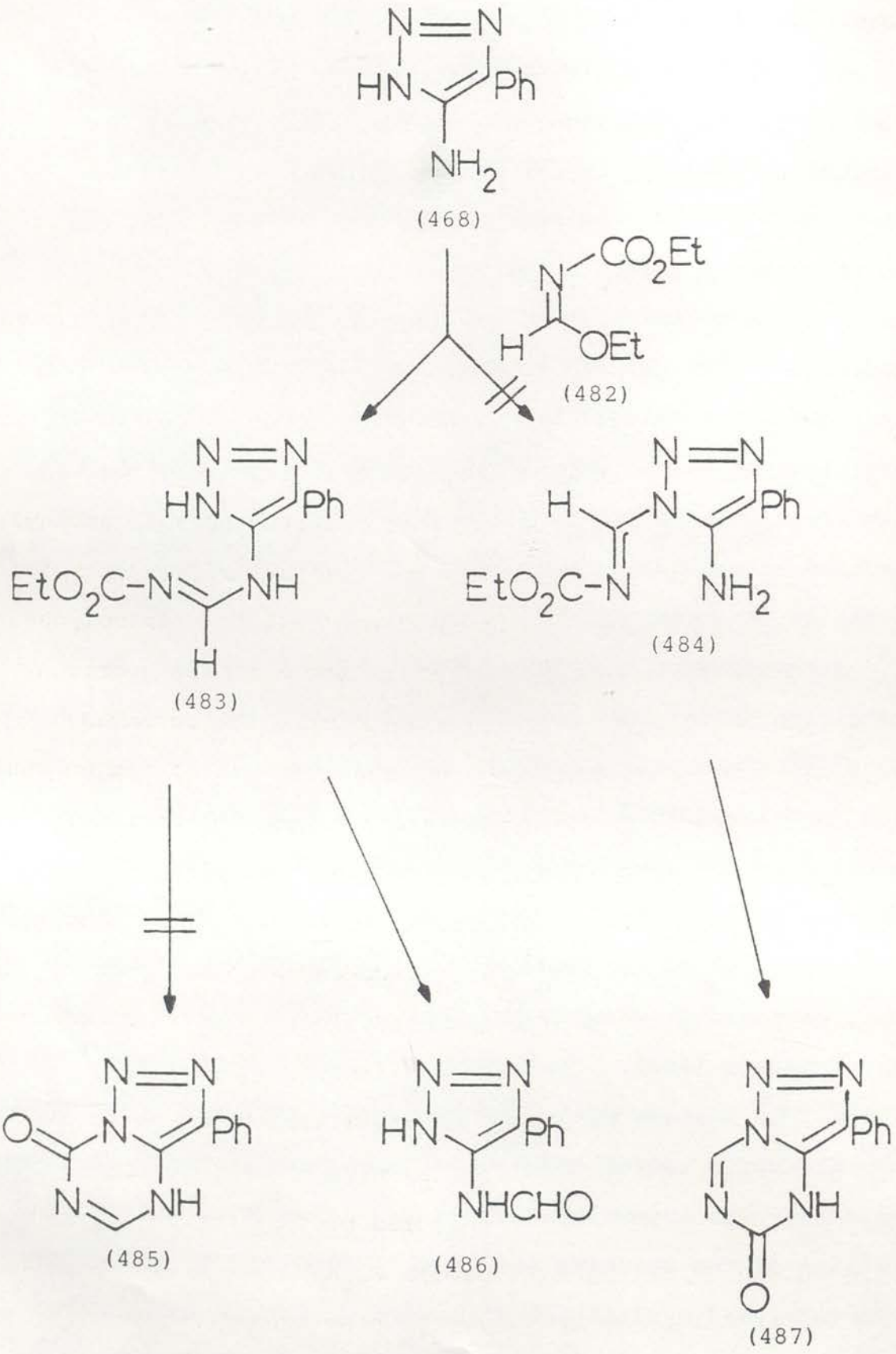
(ii) MeCONCO

(iii) Base

Scheme 121

complicated and a multicomponent mixture was produced. However the aminotriazole (468) did react smoothly with acetyl isocyanate to give a moderate yield of the acetylurea (478a) which gave analytical and spectroscopic data in accord with its assigned structure. Furthermore confirmation that the aminotriazole (468) had reacted with the isocyanate at the exocyclic amino-group in preference to reaction at the ring NH was provided by reaction of the urea (478a) with acetic anhydride. The product obtained from this reaction gave analytical and spectroscopic data consistent with a mono-acylated derivative of (478a) and in particular the appearance of a high frequency carbonyl absorption at 1755 cm^{-1} in its i.r. spectrum allowed assignment of the ring N-acetylated structure (478b) to this compound.

Attempts were then made (Scheme 121) to convert the acetylurea (478a) into the 1,2,3-triazolo[1,5-a]-1,3,5-triazin-5-one (480) via base-catalysed cyclisation. However it was also recognised that two other pathways were available for the reaction of the acetylurea (478a) with base. Thus attack of the base at the acetyl group in the side chain might result in de-acetylation to the urea (481). Alternatively attack at the urea carbonyl group might occur with hydrolysis to the aminotriazole (468). In practice the acetylurea (478a) failed to react on heating with aqueous ammonia and when it was heated with ethanolic sodium ethoxide or sodium carbonate no material whatsoever was recovered (presumably due to complete decomposition of the starting material). Moreover an attempted acid-catalysed cyclisation of the acetylurea (478a) to the triazolotriazinone (480) by heating with dilute hydrochloric

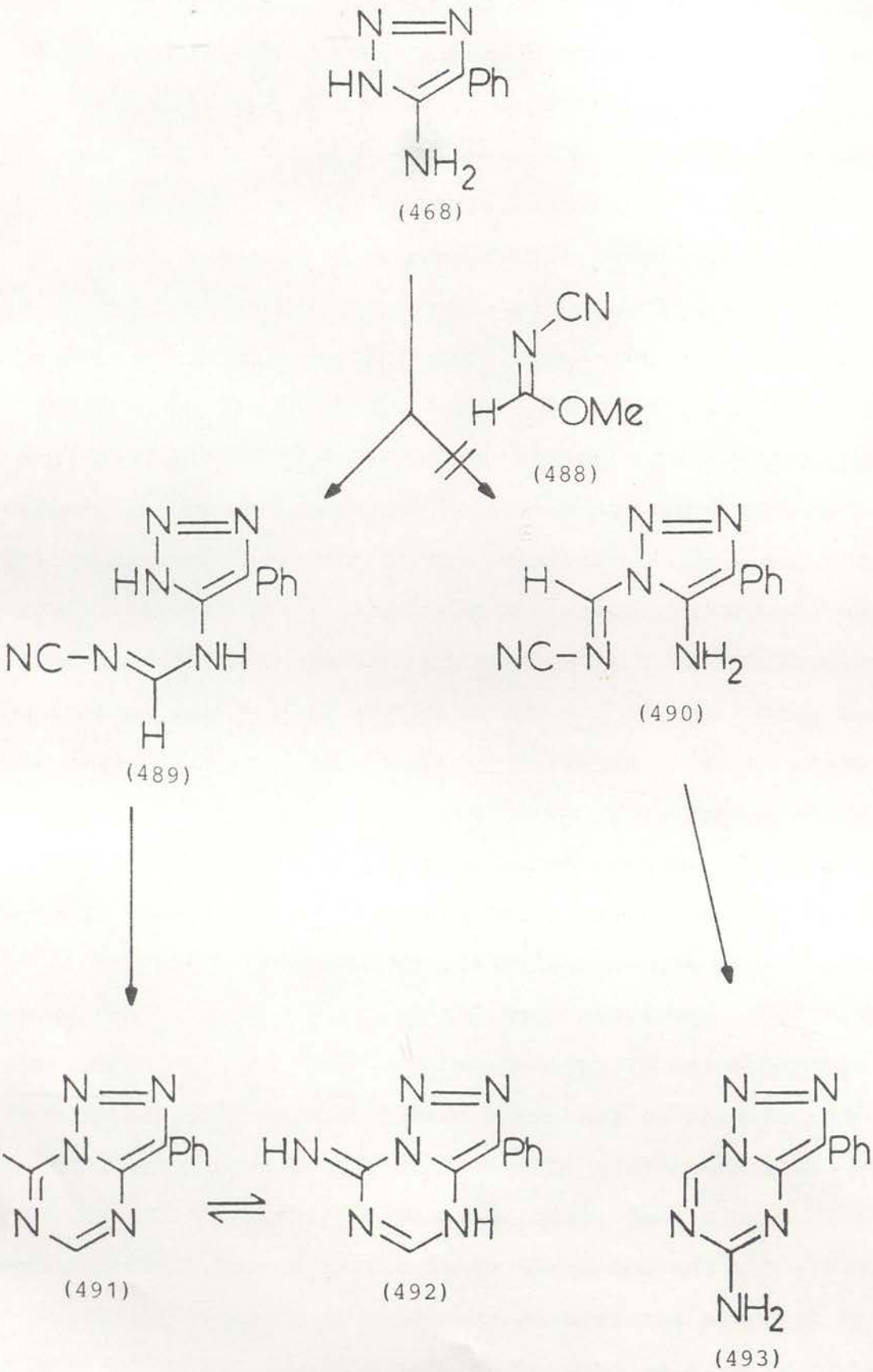


Scheme 122

acid resulted only in hydrolytic conversion into the amino-triazole (468).

An alternative synthesis (Scheme 122) of a 1,2,3-triazolo-[1,5-a]-1,3,5-triazin-5(4H)-one derivative (487) might be envisaged by reaction of the aminotriazole (468) with the ester-imidate (482). However the imidate (482) has previously been shown[173] to react with 3-aminopyrazole exclusively at the exocyclic amino-group. The reaction of the aminotriazole (468) with the imidate (482) would therefore be expected to give the 7-oxo structure (485) rather than the 5-oxo structure (487). In practice the only product isolated from this reaction was the formamide (486) whose i.r. spectrum showed NH and carbonyl absorptions at 3360-3100 and 1670 cm^{-1} respectively attributable to the formamide moiety. Elemental analysis of this compound provided the molecular formula $C_9H_8N_4O$ and its mass spectrum gave a parent ion at m/e 188 in accord with the formamide structure (486). Formation of the formamide (486) can be readily explained (Scheme 122) by condensation of the aminotriazole (468) with the imidate (482) to give the formamidine (483) followed by hydrolysis. Alternatively reaction of the amino-triazole (468) with ethyl formate produced by hydrolysis of the imidate (482) under the reaction conditions would also account for the formation of the formamide (486).

In contrast to the ester-imidate (482) the cyano-imidate (488) reacted smoothly (Scheme 123) with the aminotriazole (468) to give a good yield of a solid product which analysed correctly for the molecular formula $C_{10}H_8N_6$ and showed a parent ion in its mass spectrum at m/e 212 consistent with its formulation as 7-amino-3-phenyl-1,2,3-triazolo[1,5-a]-1,3,5-

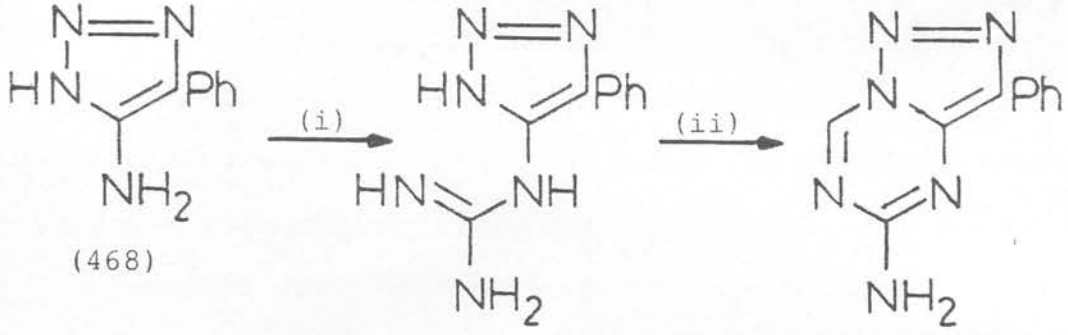


Scheme 123

triazine (491). The isomeric 5-amino structure (493) can be excluded on the basis of the known[173] aptitude of amino-azoles to react with the cyano-imidate (488) at the exocyclic amino-group. The structure (491) for the compound is further supported by its ^{1}H n.m.r. spectrum which contains a one-proton singlet at δ8.29 attributable to H-5 and a two-proton singlet at δ9.14 assignable to the amino-group. However the i.r. spectrum of the product shows a strong band at 1720 cm^{-1} attributable to the imino-substituent in the tautomeric structure (492). It is probable therefore that the product exhibits enamine-imine tautomerism [(491)$\rightleftharpoons$(492)] with the imino-form (492) predominating in the solid state and the amino-form (491) in solution. Amine-imine tautomerism of this type is well known[174] in other bridgehead-fused amino-heterocycles. Moreover Le Count and Taylor have studied the phenomenon in detail and have concluded[175] that the tautomeric equilibrium is finely balanced, imine formation being more likely as the degree of aza-substitution increases.

The formation of the 7-aminotriazolotriazine (491) rather than its 5-amino isomer (493) can be explained by the amino-triazole (468) reacting with the cyano-imidate (488) again preferentially at the exocyclic N-atom. Thus the reaction must proceed through the N-cyano intermediate (489) to give the 7-aminotriazolotriazine (491) rather than via the intermediate (490) (attack at the ring N-atom) which would have given the 5-amino isomer (493). An unambiguous synthesis of the 5-aminotriazolotriazine (493) would firmly exclude this alternative structure and such a synthesis (Scheme 124) might be possible via the triazolylguanidine (494). However attempts

to form the guanidine (494) by reacting the aminotriazole (468) with S-methylthiourea or cyanamide under a variety of conditions failed the starting material being recovered unchanged in all cases.



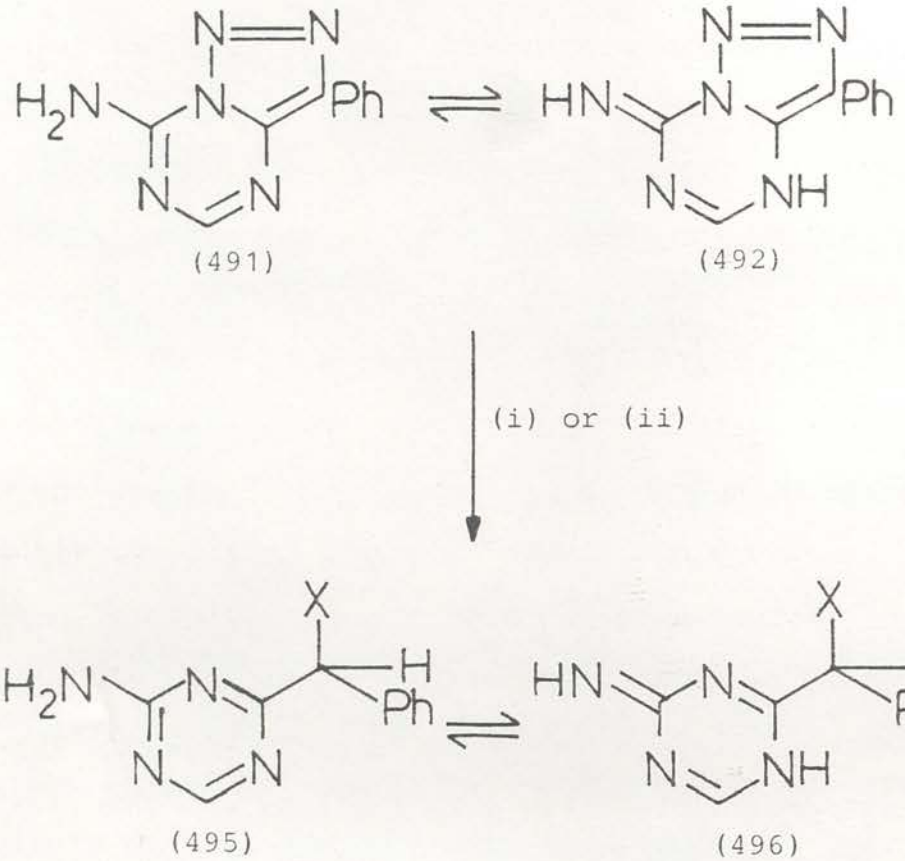
(468) (494) (493)

(i) $NH_2C(NH)SMe$ or NH_2CN

(ii) $HC(OR)_3$

Scheme 124

Having devised an efficient synthesis of the 7-amino-1,2,3-triazolo[1,5-a]-1,3,5-triazine (491) it was of interest to examine its reactivity and in particular its susceptibility to triazole ring cleavage which might thereby provide a new synthesis of 2-functionalised-4-amino-1,3,5-triazines. Not unexpectedly in view of its tautomeric structure (see before) the aminotriazolotriazine (491) failed to show simple amine-like reactivity. Thus it resisted acylation either by heating with acetic anhydride alone or in the presence of sulphuric acid. This inertness can be attributed to a reduction in the basicity of the amino-group as a consequence of imide character due to the tautomerism [Scheme 123; (491)⇌(492)]. Low basicity due to imide character also accounts for the insolubility of the aminotriazolotriazine (491) in cold concentrated hydrochloric acid and its failure to undergo diazotisation. The aminotriazolotriazine (491) was soluble in phosphoric acid but attempted



X

a; OAc

b; Cl

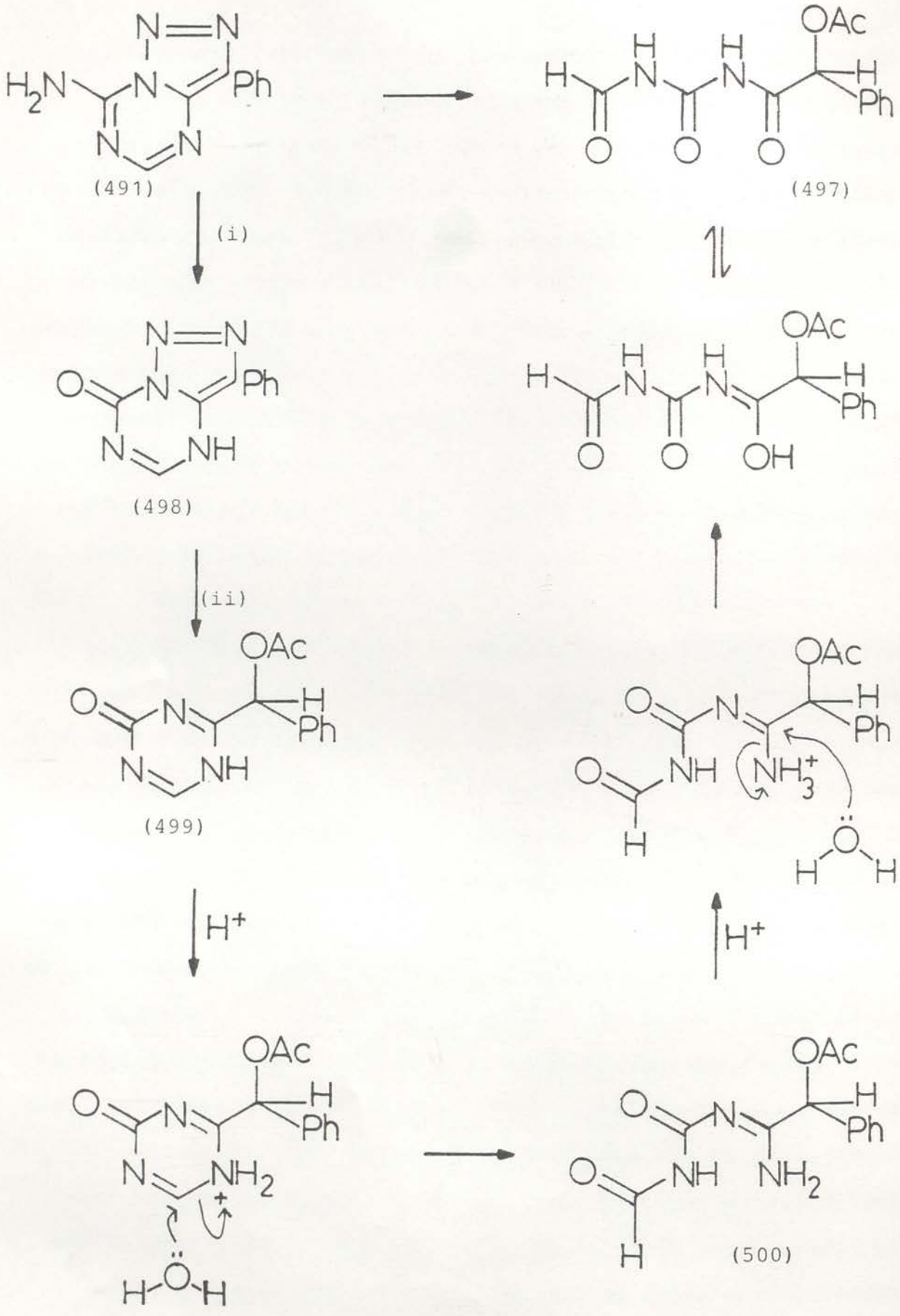
(i) AcOH

(ii) AcOH-AcCl

Scheme 125

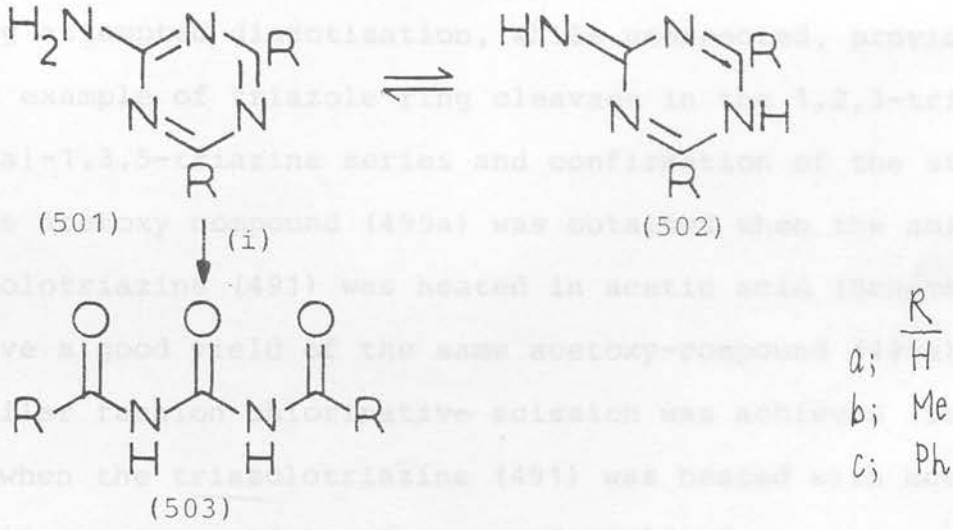
diazotisation using sodium nitrite in a mixture of phosphoric and glacial acetic acid gave no isolable material. On the other hand treatment of the aminotriazolotriazine (491) with sodium nitrite in glacial acetic acid (Scheme 125) gave a readily separated mixture of two products. The i.r. spectrum of the major product showed an ester-type carbonyl absorption at 1750 cm^{-1} and this together with the appearance of a benzylic proton resonance at δ6.38 in its ^1H n.m.r. spectrum suggested that triazole ring cleavage had occurred rather than diazotisation. Elemental analysis and mass spectral evidence agreed on the molecular formula $C_{12}H_{12}N_4O_2$ (m/e 244) and the product was therefore assigned the acetoxybenzyltriazine structure (495a).

The minor product also isolated from the attempted diazotisation of the aminotriazolotriazine (491) in glacial acetic acid showed NH (3260 and 3160 cm^{-1}) and carbonyl absorption (1750 and 1680 cm^{-1}) in its i.r. spectrum and gave analytical and mass spectral data consistent with the molecular formula $C_{12}H_{12}N_2O_5$ (m/e 264). Although lack of material prevented a ^1H n.m.r. spectrum being obtained it is obvious from the molecular formula that the product lacks both the triazole and the triazine rings and probably has an open chain structure which can be tentatively formulated as [Scheme 126; (497)]. Formation of this product can be explained by a series of transformations of the aminotriazolotriazine (491) as outlined in Scheme 126. Thus deamination of the aminotriazolotriazine (491) by initial diazotisation and subsequent hydrolysis could afford the triazolotriazinone (498) which under the acidic conditions of the diazotisation might be further converted via triazole ring scission to the acetoxybenzyltriazinone (499). Acid catalysed



Scheme 126

hydrolysis of the triazinone ring of (499) would give the amidine (500) and yet further hydrolysis of the latter would complete the transformation to the linear product (497). Moreover although this conversion may appear drastic at first sight a similar conversion has been reported in the literature.[176] [177] Thus (Scheme 127) the 2-amino-4,6-dialkyl-1,3,5-triazines (501b) and (501c) were shown to convert upon attempted diazotisation into the corresponding linear di-acylureas (503b) and (503c).



(i) HNO_2

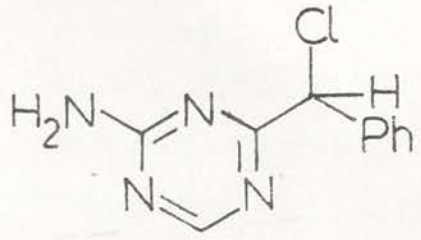
Scheme 127

The unexpected isolation of the two products, the acetoxybenzyltriazine [Scheme 125; (495a)] and the di-acylurea [Scheme 126; (497)] from the attempted diazotisation of the aminotriazolotriazine (491) not only shows the reactivity of the 1,2,3-triazolo[1,5-a]-1,3,5-triazine system towards triazole scission but also shows that the major product of this reaction, the aminotriazine (495a), is resistant to diazotisation. It might therefore be inferred that the aminotriazine derivative (495a) exists as the imine tautomer (496a) and further support for this inference is provided by the i.r. spectrum of the

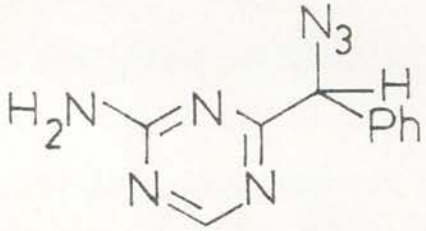
compound which contains bands at 1750 and 1680 cm^{-1} the former being attributable to the acetoxy-substituent and the latter to the imino group. Burger and Hornbaker[178] have previously shown (Scheme 127) that 2-amino-1,3,5-triazine (501a) fails to undergo common amine reactions and they therefore conclude that this compound exists largely in the imine tautomeric form (502a). For similar reasons Beyer *et al* [176] have suggested that 2-amino-4,6-dimethyl-1,3,5-triazine (501b) also exists as the imine tautomer (502b).

The formation of the acetoxy-compound [Scheme 125; (495a)] during attempted diazotisation, while unexpected, provided the first example of triazole ring cleavage in the 1,2,3-triazolo-[1,5-a]-1,3,5-triazine series and confirmation of the structure of the acetoxy compound (495a) was obtained when the amino-triazolotriazine (491) was heated in acetic acid (Scheme 125) to give a good yield of the same acetoxy-compound (495a). In a similar fashion chlorinative scission was achieved (Scheme 125) when the triazolotriazine (491) was heated with acetyl chloride-acetic acid to give a good yield of the chlorobenzyl-aminotriazine (495b). Analytical and spectroscopic data for this compound are consistent with the structure (495b) with the exception of the i.r. spectrum which shows an absorption at 1670 cm^{-1} and thus suggests that the compound exists as its imine tautomer (496b) at least in the solid state. In contrast the chloro-compound (495b) was not obtained when the triazolo-triazine (491) was stirred with cold concentrated hydro-chloric acid and instead a complex mixture was formed.

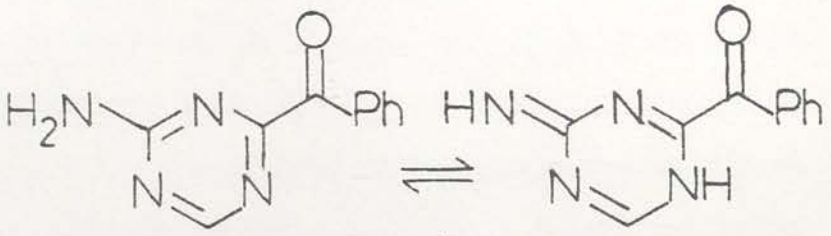
With the objective (Scheme 128) of obtaining the azide (504) the reaction of the chloro-compound (495b) with sodium



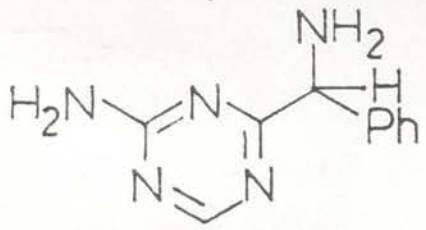
(495b)



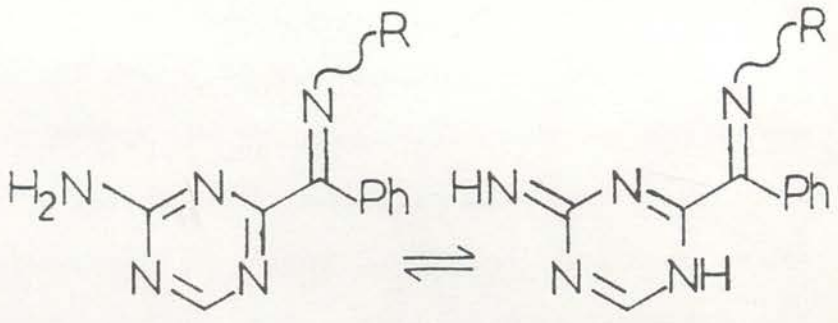
(504)



(505) (506)



(507)



(508) (509)

R

a; OH
b; NH_2
c; NHPh

(i) NaN_3

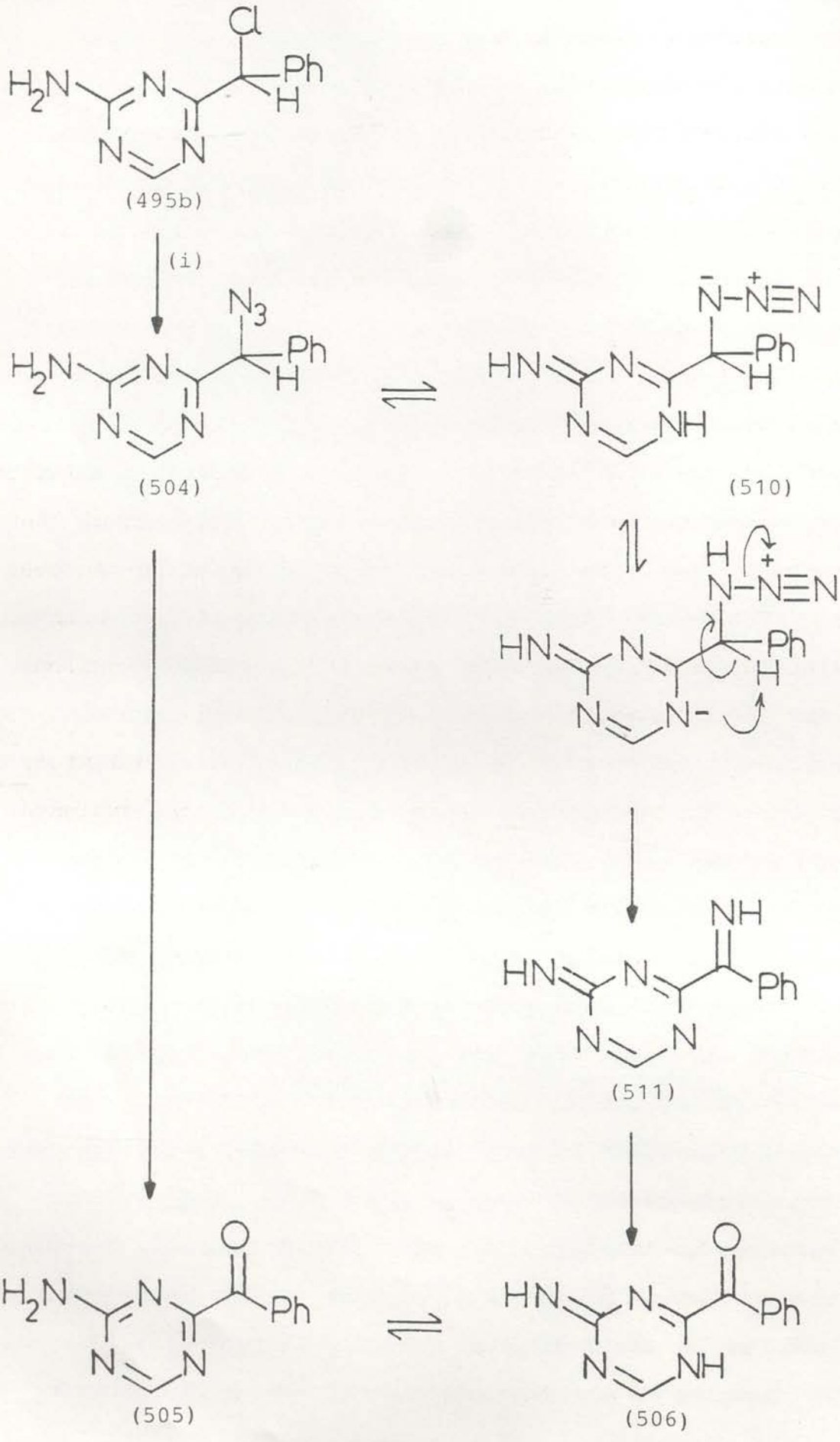
(ii) [H]

(iii) RNH_2

Scheme 128

azide in aqueous ethanol was next investigated. The azide (504) was required as a source, by reduction, of the amine (507) needed in turn for elaboration into imidazo[1,5-a]-1,3,5-triazine derivatives. Heating the chloro-compound (495b) with sodium azide gave a fair yield of a fawn product whose i.r. spectrum lacked the anticipated azide absorption and instead displayed bands at 1715 and 1690 cm^{-1} in the carbonyl region. Moreover the product gave analytical and mass spectral data consistent with the molecular formula $C_{10}H_8N_4O$ (m/e 200) and its ^1H n.m.r. spectrum lacked any resonance attributable to a benzylic proton but only showed signals due to the protons of a phenyl group and a one-proton singlet assigned to H-6. On the basis of this evidence the product is assigned the tautomeric 4-amino-2-benzoyl-1,3,5-triazine structure [(505)⇌(506)]. The isolation of the ketone (505) from the reaction of the chloro-compound (495b) with sodium azide is explicable as outlined in Scheme 129. The initial product of the reaction must almost certainly be the azide (504) in equilibrium with the imine tautomer (510) however this product cannot be stable under the reaction conditions and decomposes to give the ketone (505). An acid-catalysed decomposition of the azido-group of (510) would afford the imine (511) and subsequent hydrolysis of this compound would account for the formation of the ketone (506) and its amine tautomer (505). Clearly the acidity of the ring NH in the azidobenzyliminotriazine (510) could promote this transformation by catalysing the breakdown of the azide moiety and a similar mechanism has been proposed for the analogous transformation in the pyrimidine series (see Chapter 3).

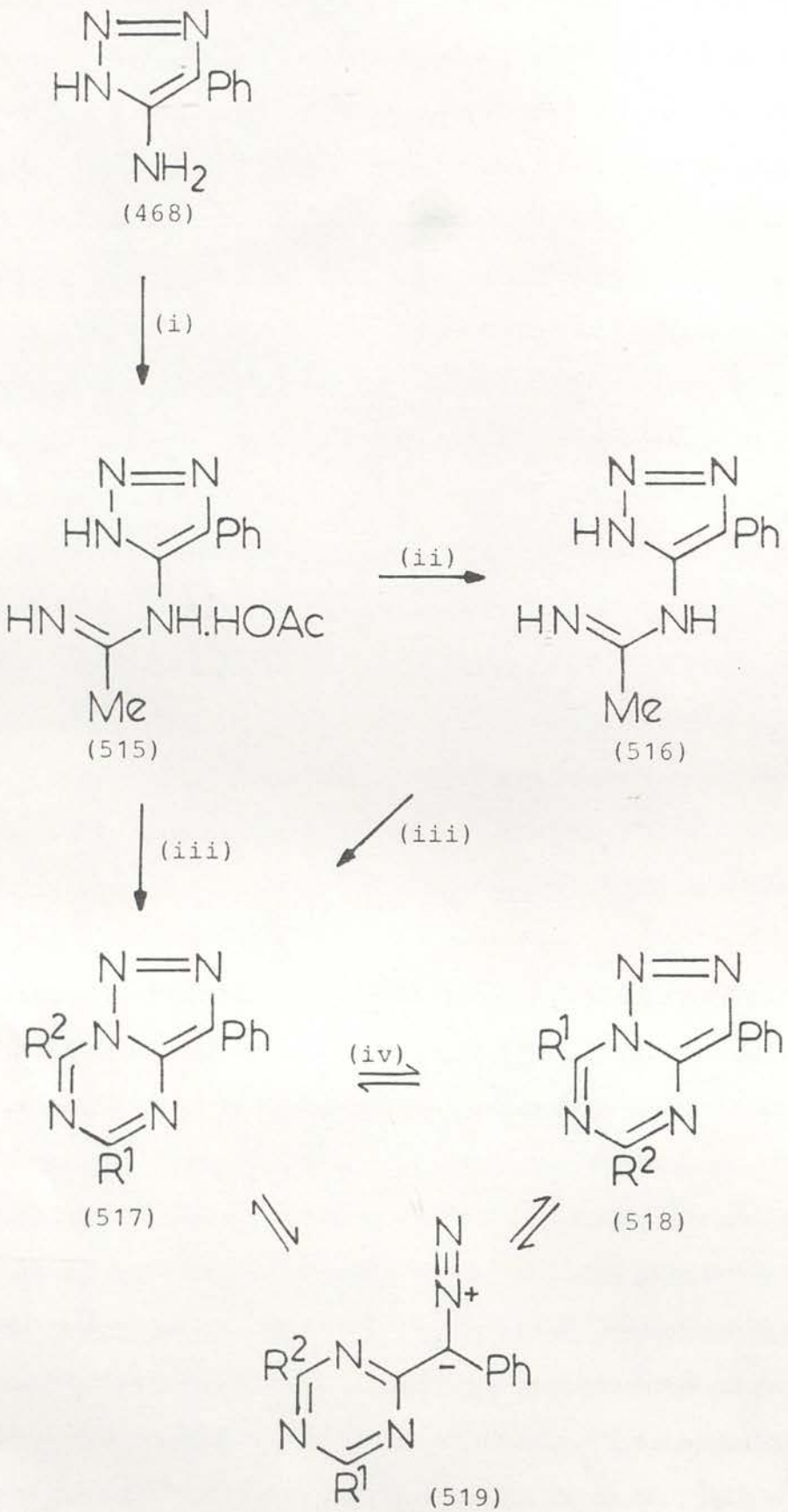
Few examples of acyl-1,3,5-triazines have been reported



Scheme 129

in the literature[179] and it was therefore of interest to investigate the reactivity of the 4-amino-2-benzoyl-1,3,5-triazine [Scheme 128; (505)⇌(506)] particularly towards the usual carbonyl reagents. It was found that the ketone (505) reacted readily (Scheme 128) with hydroxylamine to give a good yield of a product whose analytical and mass spectral properties are consistent with the oxime structure (508a). However whereas the ^1H n.m.r. spectrum of the oxime contained a two-proton singlet at δ7.60 attributable to an NH_2 moiety and hence suggests that the amino-tautomer (508a) predominates in solution the i.r. spectrum of the product contains an absorption at 1660 cm^{-1} possibly due to the ring imine group of the imino-tautomer (509a). The ketone (505) reacted in a similar fashion with hydrazine and phenylhydrazine (Scheme 128) to afford excellent yields of the tautomeric hydrazone [(508b)⇌(509b)] and phenylhydrazone [(508c)⇌(509c)] both of which gave analytical data and spectroscopic properties consistent with the assigned structures.

As the instability (Scheme 129) of the azidobenzylamino-triazine (504) is thought to be a result of the acidity of the imine tautomer (510) catalysing decomposition of the azide group attention was next directed towards preparation of 5,7-dialkyl representatives of the 1,2,3-triazolo[1,5-a]-1,3,5-triazine ring system with the hope that 5,7-dialkyl-1,2,3-triazolo-[1,5-a]-1,3,5-triazine derivatives might be transformed into 4,6-dialkyl-1,3,5-triazines bearing a functionalised alkyl group in the 2-position. Furthermore, as a 4,6-dialkyl-1,3,5-triazine derivative would not have any potential acidity the corresponding 2-azidoalkyl compounds could be stable and might therefore be



	R^1	R^2
a;	Me	Me
b;	Me	H

(i) MeC(NH)OEt-AcOH

(ii) $NaHCO_3$

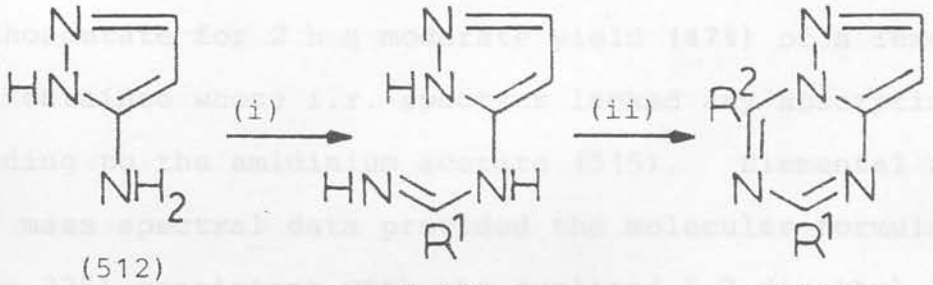
(iii) $R^2C(OEt)_3$

(iv) heat

Scheme 131

converted, by reduction, into the key intermediate 2-amino-alkyl-4,6-dialkyl-1,3,5-triazines required as precursors for the synthesis of the imidazo[1,5-a]-1,3,5-triazine ring system.

Novinson and his co-workers have shown[180] (Scheme 130) that the aminopyrazole (512) can be converted into a pyrazolo[2,3-a]-1,3,5-triazine derivative (514) by a two step sequence via an intermediate amidine (513). Thus treatment of the aminopyrazole (512) with an imidate followed by reaction of the resulting amidine with an ortho-ester allowed sequential incorporation



(512) (513) (514)

(i) $R^1C(NH)OEt$

(ii) $R^2C(OEt)_3$

Scheme 130

of two alkyl groups at the 5- and 7-positions of the pyrazolo-triazine nucleus. It was therefore of interest to investigate the extension of this sequence (Scheme 131) to the aminotriazole (468).

When the aminotriazole (468) was reacted with ethyl acetimidate in the presence of acetic acid a fair yield of a colourless solid product was obtained whose i.r. spectrum showed a broad absorption at 2800-2300 cm^{-1} suggesting that it was a salt. Although elemental analysis provided the molecular formula $C_{12}H_{12}N_5O_2$ (m/e 261) consistent with the acetamidinium acetate structure (515) the mass spectrum of the product gave a

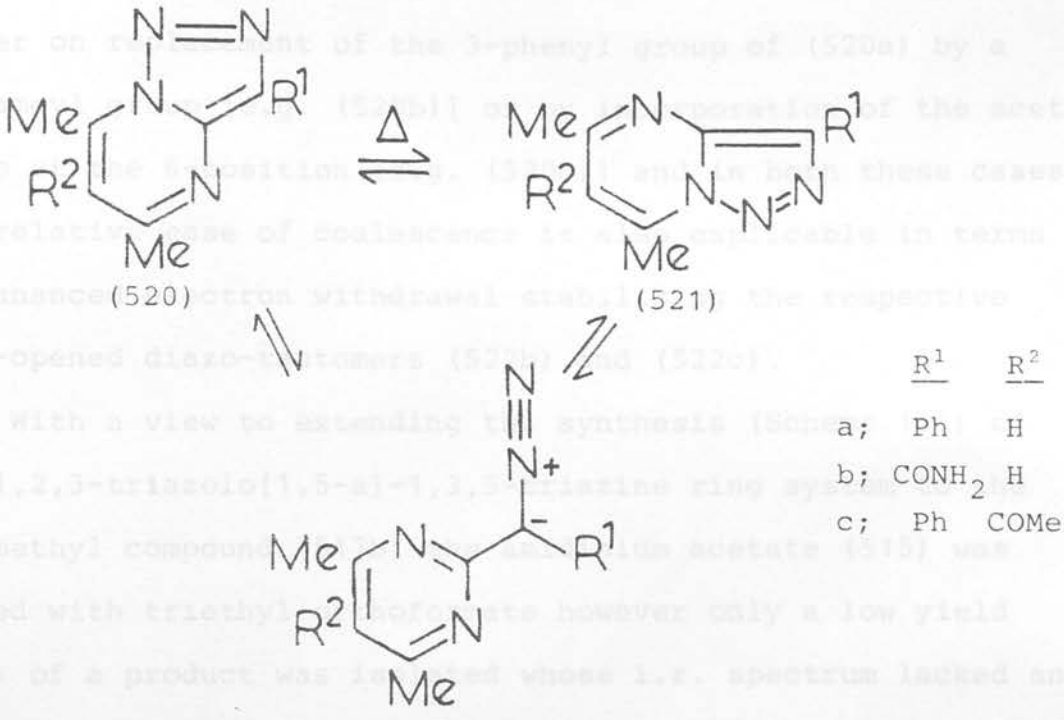
parent ion at m/e 201 and this is explicable in terms of loss of acetic acid in the mass spectrometer. Further support for the structure (515) was obtained from the ^{1}H n.m.r. spectrum of the product which contained three-proton singlets at δ2.08 and δ1.90 attributable to the acetamidine methyl group and the acetate ion respectively. Moreover when the amidinium acetate (515) was treated with sodium bicarbonate a quantitative yield of the free amidine (516) was obtained and analytical and spectroscopic data for the amidine (516) were completely in accord with its assigned structure.

When the amidinium acetate (515) was heated with triethyl orthoacetate for 2 h a moderate yield (47%) of a lemon product was obtained whose i.r. spectrum lacked any absorption corresponding to the amidinium acetate (515). Elemental analysis and mass spectral data provided the molecular formulae $C_{12}H_{11}N_5$ (m/e 225) consistent with the cyclised 5,7-dimethyl-3-phenyl-1,2,3-triazolo[1,5-a]-1,3,5-triazine structure (517a) and the ^{1}H n.m.r. spectrum of the product confirmed this structure showing three-proton singlets at δ3.02 and δ2.72 assigned to the C-7 and the C-5 methyl groups respectively (on the basis that the C-7 methyl group will give rise to the more deshielded signal as a consequence of being adjacent to an electron deficient bridgehead nitrogen atom). The lowish yield of the isolated triazolotriazine (517a) under these conditions was however disappointing and prompted attempts to optimise the formation of the product (517a). On the basis that the reduced yield of product isolated might be due to its thermal or chemical decomposition once formed (no starting material being recovered) the amidinium acetate (515) was stirred with triethyl ortho-

acetate at room temperature for 19 h. However no reaction was observed under these conditions and a similar inertness to reaction was observed when the free amidine (516) was heated with triethyl orthoacetate for 2 h. The observed difference in reactivity between the amidinium acetate (515) and its free base (516) towards cyclisation with triethyl orthoacetate can be accounted for by acid catalysis of the reaction by the acetic acid present in the former case. Thus when toluene-p-sulphonic acid was added to the heated mixture of the free amidine (516) and triethyl orthoacetate reaction did occur although a complex mixture was formed from which the desired triazolotriazine (517a) was isolated only in low yield (16%). However when the amidinium acetate (515) was heated with triethylorthoacetate for 20 min rather than 2 h the isolated yield of the triazolotriazine (517a) was increased from 47% to 59%. Furthermore when the reaction was repeated with heating only for the minimum time required to dissolve starting acetate (515) (i.e. 5 min) the triazolotriazine (517a) was obtained in very good yield (77%) and this behaviour is explicable in terms of a rapid acid-catalysed thermal cyclisation of the acetamidinium acetate (515) to the product (517a) followed by a slower acid-catalysed decomposition of the product.

Diazoalkylideneamine-1,2,3-triazole tautomerism has been reported[80] to occur (Scheme 132) for 5,7-dimethyl-3-phenyl-1,2,3-triazolo[1,5-a]pyrimidine [(520a)$\rightleftharpoons$(521a)] at elevated temperatures and as the triazolotriazine [Scheme 131; (517a)] is a direct 6-azalogue of this compound it was of interest to investigate the possibility of similar ring-chain tautomerism in the 1,2,3-triazolo[1,5-a]-1,3,5-triazine series. The i.r.

spectrum of the triazolotriazine (517a) lacks diazo absorption at *ca* 2200 cm^{-1} demonstrating that at room temperature

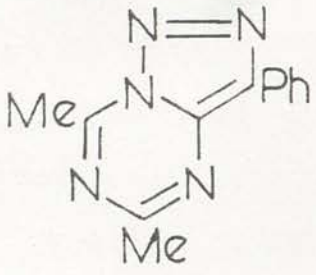


Scheme 132

it exists entirely in the fused-triazole form. Thus at room temperature the ^1H n.m.r. spectrum of (517a) exhibits singlets at δ3.02 and δ2.72 attributable to the non-equivalent C-7 and C-5 methyl groups. However on warming, both singlets progressively broaden and ultimately coalesce at 97° before sharpening up to a singlet centred at δ2.87. These changes, which reversed on cooling, are attributed to the rapid interconversion [Scheme 131; (517a)⇌(518a)] proceeding through the open-chain diazo-tautomer (519a) at elevated temperature. Moreover the significantly lower coalescence temperature (97°) of the triazolotriazine (517a) to that reported[80] for the analogous triazolopyrimidine [Scheme 132; (520a)] (>150°) is consistent with the enhanced stabilisation of the diazo-tautomer (519a)

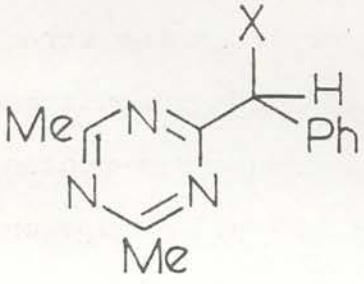
resulting from the increased electron withdrawal of the 1,3,5-triazine ring compared to a pyrimidine ring. In the pyrimidine series a similar effect is observed (Scheme 132) either on replacement of the 3-phenyl group of (520a) by a carbamoyl group [e.g. (520b)] or by incorporation of the acetyl group at the 6-position [e.g. (520c)] and in both these cases the relative ease of coalescence is also explicable in terms of enhanced electron withdrawal stabilising the respective ring-opened diazo-tautomers (522b) and (522c).

With a view to extending the synthesis (Scheme 131) of the 1,2,3-triazolo[1,5-a]-1,3,5-triazine ring system to the monomethyl compound (517b) the amidinium acetate (515) was heated with triethyl orthoformate however only a low yield (14%) of a product was isolated whose i.r. spectrum lacked any absorption attributable to the acetate starting material (515). Although satisfactory elemental analyses could not be obtained for the product its mass spectrum gave a parent ion at m/e 211 consistent with the desired triazolotriazine structure (517b) and further support for this structure was obtained from the ^{1}H n.m.r. spectrum of the compound which, as well as showing signals due to a phenyl group, contained a three-proton singlet at δ3.16 and a one-proton singlet at δ8.69 assigned to the C-5 methyl group and H-7 respectively. However the isomeric 7-methyl structure (518b), derivable from the 5-methyl structure (517b) by Dimroth rearrangement, cannot be excluded and in fact the relatively deshielded position of the methyl resonance suggests that the 7-methyl structure (518b) may be more likely. Attempts to increase the yield of the monomethyl triazolotriazine (517b) by heating the acetamidinium acetate (515) with

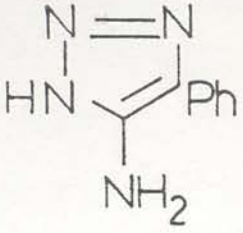


(517a)

(i) (ii)



(523)



(468)

X

a; OAc

b; Cl

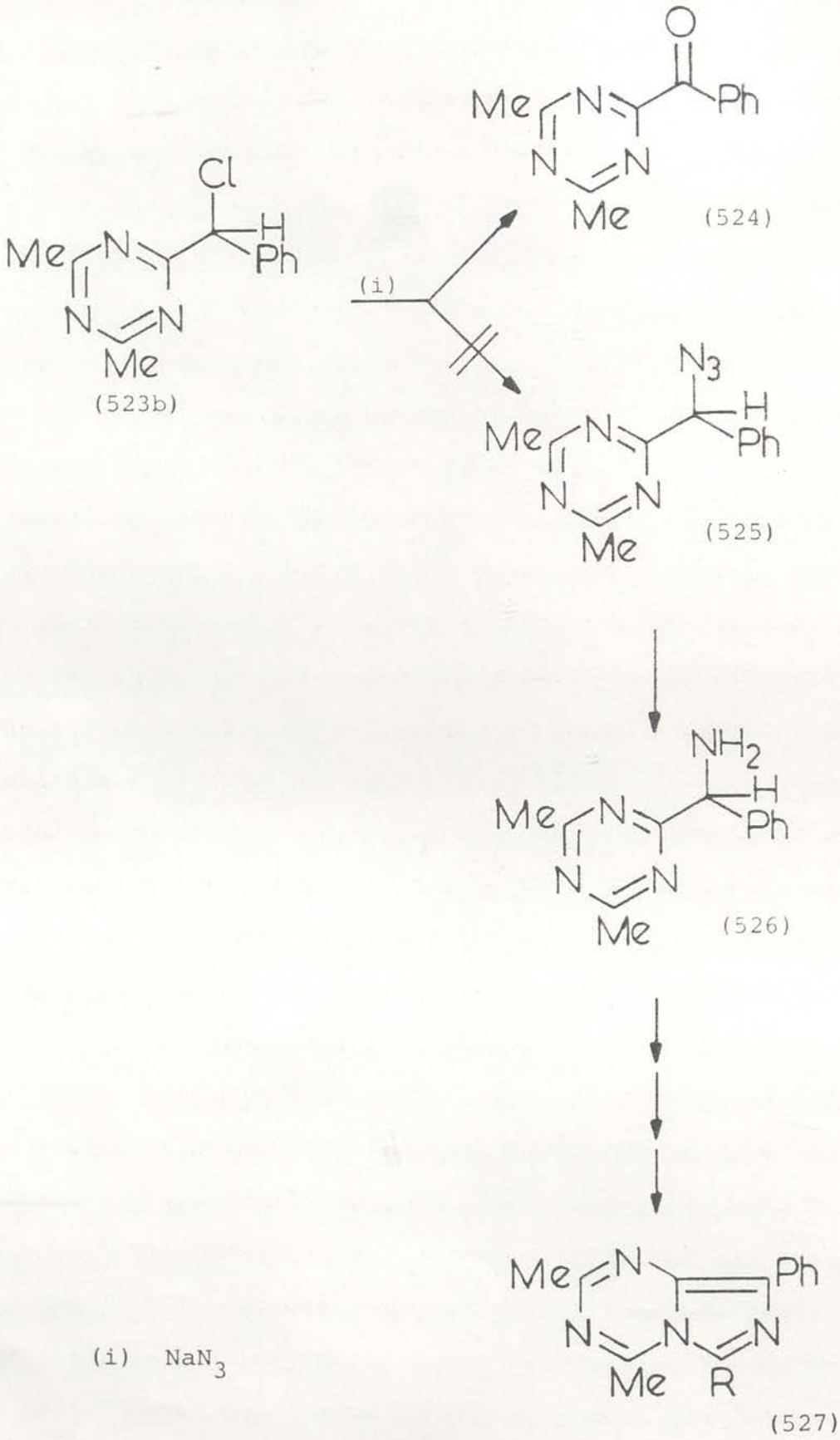
(i) AcOH or AcOH-AcCl

(ii) conc. HCl

Scheme 133

triethyl orthoformate only until the latter had dissolved or by reacting the free acetamidine (516) with triethyl orthoformate failed only complex gums being obtained in both cases.

Having devised an efficient route to the 5,7-dimethyl-3-phenyl-1,2,3-triazolo[1,5-a]-1,3,5-triazine (517a) it was of interest to compare its reactivity towards triazole-ring scission with that of its 6-deaza analogue, 5,7-dimethyl-3-phenyl-1,2,3-triazolo[1,5-a]pyrimidine [Scheme 132; (520a)] (see Chapter 2). Thus the triazolotriazine (517a) was heated (Scheme 133) in glacial acetic acid to give a good yield of a colourless solid whose i.r. spectrum exhibited the expected acetoxy carbonyl absorption at 1735 cm^{-1}. Analytical and mass spectral data indicated the molecular formula $C_{14}H_{15}N_3O_2$ (m/e 257) in accord with the acetoxybenzyltriazine structure (523a). The ^1H n.m.r. spectrum of the product confirmed that triazole-ring scission had occurred showing a six-proton singlet at δ2.58 attributable to the equivalent methyl groups on the triazine ring and a three-proton singlet at δ2.21 assigned to the acetoxy group. However whereas scission of the triazole ring of the triazolotriazine (517a) occurred smoothly on heating with acetic acid chlorinative scission proved to be less straightforward. Thus when the triazolotriazine (517a) was stirred with concentrated hydrochloric acid (Scheme 133) instead of the expected chlorobenzyltriazine (523b) the only product isolated was the aminotriazole (468). Evidently acid-catalysed hydrolysis of the 1,3,5-triazine ring occurred in preference to acid-promoted scission of the 1,2,3-triazole ring and although such hydrolytic decomposition has been long known[181,182] for trisubstituted 1,3,5-triazines in general drastic conditions



(i) NaN_3

Scheme 134

(i.e. concentrated hydrochloric acid at 150-225°) are normally required. In contrast when the triazolotriazine (517a) was heated with acetyl chloride-acetic acid an exclusive cleavage of the triazole ring occurred to afford the chloro-compound (523b) in excellent yield accompanied by a small amount of the acetoxy-compound (523a). Analytical and mass spectral data were entirely consistent with the assignment of the major product as the chloro-compound (523b) in particular the ^{1}H n.m.r. spectrum showing a benzylic proton signal at δ5.91.

Having the 2-(α-chlorobenzyl)-4,5-dimethyl-1,3,5-triazine (523b) in hand it was hoped that conversion of this compound (Scheme 134) to the corresponding azide (525) and then by reduction to the amine (526) required as a key intermediate for the synthesis of imidazo[1,5-a]-1,3,5-triazine derivatives (527) might be straightforward. In practice when the chloro-compound (523b) was heated under reflux with sodium azide in aqueous ethanol a multicomponent mixture resulted. Repetition of the above reaction at room temperature gave a colourless oily product whose i.r. spectrum contained the anticipated triple bond absorption at 2100 cm^{-1}. However the ^{1}H n.m.r. spectrum of the oil contained benzylic proton signals at δ5.91 and δ5.52 suggesting that it was a mixture of the starting chloro-compound (523b) and the desired azide (525) with the former predominating in the ratio 3:2 and it was not possible to separate this mixture. An attempt to cause the reaction to go to completion by doubling the excess of sodium azide employed and prolonging the reaction did not result in the formation of the azide (525). Instead a different product was obtained whose i.r. spectrum lacked azide absorption at *ca* 2100 cm^{-1} but contained a carbonyl

absorption at 1690 cm^{-1}. Elemental analysis and mass spectral data provided the molecular formula $C_{12}H_{11}N_3O$ (m/e 213) consistent with ketone structure (524) and confirmation of this assignment was provided by the ^1H n.m.r. spectrum of the compound which lacked any resonance attributable to a benzylic proton. Clearly the azide (525) is formed initially but is unstable even in the absence of any potentially acidic groups and decomposes with hydrolysis to give the ketone (524). The instability of the required intermediate 2-azidobenzyl-1,3,5-triazine compounds shown throughout this section thus prevented the synthesis of imidazo[1,5-a]-1,3,5-triazine derivatives via the proposed route.

4.2 Experimental

Ethoxycarbonyl Isothiocyanate

A suspension of potassium thiocyanate (19.4 g, 0.2 mol) (dried by azeotroping with absolute ethanol) in dry acetonitrile (70.0 ml) was stirred and heated to 100° (steam bath). Freshly distilled ethyl chloroformate (21.7 g, 0.2 mol) was added in portions whereupon the suspension thickened and a yellow colouration developed. The heat source was removed and, after cooling, the mixture was filtered to remove potassium chloride and the inorganic residue was washed with dry acetonitrile. The combined filtrate and washings were evaporated under high vacuum at room temperature to yield ethoxycarbonyl isothiocyanate (18.9 g; 72%) as an orange oil, ν_{max} 1980 (N=C=S) and 1750 (CO) cm^{-1} (lit.,[183,184] ν_{max} 1990-1960 (N=C=S) and 1750 (CO) cm^{-1}]. Supportive evidence for the exclusive formation of ethoxycarbonyl isothiocyanate rather than the isomeric ethoxycarbonyl thiocyanate was provided by the absence in the i.r. spectrum of the product of any absorption [lit.,[183,184] ν_{max} 2190 (C≡N) and 1770 (CO) cm^{-1}] attributable to this compound.

The Reaction of 5-Amino-4-phenyl-1H-1,2,3-triazole (468) with Ethoxycarbonyl Isothiocyanate

(a) A solution of the aminotriazole (468) (1.6 g, 0.01 mol) in dry 1,2-dimethoxyethane (80.0 ml) was treated with freshly prepared ethoxycarbonyl isothiocyanate (1.3 g, 0.01 mol) and the mixture was stirred at room temperature for 24 h. A second portion of ethoxycarbonyl isothiocyanate (1.3 g, 0.01 mol) was added and stirring was continued for a further 20 h. Evaporation

of the mixture gave an orange syrup which was subjected to flash chromatography in methylene chloride-ethyl acetate (2:1) over silica to afford N-ethoxycarbonyl-N'-(4-phenyl-1H-1,2,3-triazol-5-yl)thiourea (469a), (1.9 g; 65%) which formed lemon crystals, m.p. 170-171° (from toluene), ν_{max} 3300, 3230, and 3160 (NH) and 1725 (CO) cm^{-1}, $\delta(CDCl_3)$ 15.00-14.00 (1H, bs, NH), 11.10 (1H, bs, NH), 9.65 (1H, bs, NH), 7.70-7.60 (2H, m, ArH), 7.40-7.20 (3H, m, ArH), 4.18 (2H, q, J7Hz, CH_2) and 1.23 (3H, t, J7Hz, CH_3).

Found: C, 49.8; H, 4.6; N, 24.0%; M^+, 291.
$C_{12}H_{13}N_5O_2S$ requires: C, 49.5; H, 4.5; N, 24.1%; M, 291.

A second fraction was obtained as a yellow oil and shown by t.l.c. in methylene chloride-ethyl acetate (1:1) over silica to be a two component mixture containing further product. The oil was not further investigated.

(b) Repetition of the reaction described in (a) on a larger scale (0.04 mol) gave together with the desired product (469a) (yield 52%) a by-product, identified as N-ethoxycarbonyl-N'-(1-ethoxycarbonyl-4-phenyl-1,2,3-triazol-5-yl)thiourea (469c), (0.95 g; 7%), which formed colourless needles, m.p. 163-165° (from toluene), ν_{max} 3160 (NH) and 1785 and 1730 (CO) cm^{-1}, $\delta(CDCl_3)$ 8.56 (1H, bs, NH), 7.90-7.70 (2H, m, ArH), 7.50-7.35 (3H, m. ArH), 4.62 (2H, q, J7Hz, CH_2), 4.35 (2H, q, J7Hz, CH_2), 1.50 (3H, t, J7Hz, CH_3) and 1.31 (3H, t, J7Hz, CH_3).

Found: C, 49.4; H, 4.7; N, 19.6%; M^+, 363.
$C_{15}H_{17}N_5O_4S$ requires: C, 49.6; H, 4.7; N, 19.3%; M, 363.

N-Ethoxycarbonyl-N'-(1-acetyl-4-phenyl-1H-1,2,3-triazol-5-yl)-thiourea (469b)

The thiourea (469a) (0.29 g, 0.001 mol) was treated dropwise at room temperature with acetic anhydride (0.5 ml) and the pasty mass was heated at 100° (steam bath) until all of the solid had dissolved (3-4 min). The mixture was cooled, diluted with ether (5.0 ml) and filtered to afford a solid which was combined with further material obtained by evaporating the filtrate to give N-ethoxycarbonyl-N'-(1-acetyl-4-phenyl-1H-1,2,3-triazol-5-yl)thiourea (469b), (total 0.28 g; 83%) which formed colourless plates, m.p. 153-155° (from toluene-b.p. 80-100° light petroleum), ν_{max} 3240-3160 (NH) and 1770 and 1720 (CO) cm^{-1}, $\delta(CDCl_3)$ 11.31 (1H, bs, NH), 8.30 (1H, bs, NH), 7.90-7.70 (2H, m, ArH), 7.50-7.40 (3H, m, ArH), 4.31 (2H, q, J7Hz, CH_2), 2.83 (3H, s, CH_3) and 1.35 (3H, t, J7Hz, CH_3).

Found: C, 50.6; H, 4.7; N, 20.9%; M^+, 333.
$C_{14}H_{15}N_5O_3S$ requires: C, 50.5; H, 4.5; N, 21.0%; M, 333.

3-Phenyl-1,2,3-triazolo[1,5-a]-1,3,5-triazin-7(6H)-one-5(4H)-thione (471) and 3-phenyl-1,2,3-triazolo[1,5-a]-1,3,5-triazin-5(4H)-one-7(6H)-thione (472).

(a) A solution of the thiourea (469a) (1.16 g, 0.004 mol) in absolute ethanol (15.0 ml) was treated with a solution of sodium (0.18 g, 0.008 g.atom) in absolute ethanol (15.0 ml) and the mixture was heated under reflux for 3 h. Evaporation gave a pink residue which was dissolved in water (20.0 ml) and the solution was acidified with 2M aqueous hydrochloric acid to give a solid mixture of the 1,2,3-triazolo-1,3,5-triazine derivatives

(471) and (472) (0.89 g; 91%), ν_{max} 1770 and 1710 (CO) cm^{-1}. Crystallisation of this mixture afforded 3-phenyl-1,2,3-triazolo-[1,5-a]-1,3,5-triazin-5(4H)-one-7(6H)-thione (472), (0.53 g, 55%) which formed colourless needles, m.p.>360° (from ethanol), ν_{max} 3600-3300 (NH) and 1710 (CO) cm^{-1}, δ[$(CD_3)_2SO$] 13.50-12.50 (1H, bs, NH), 9.00-7.80 (1H, bs, NH), 7.80-7.65 (2H, m, ArH) and 7.60-7.20 (3H, m, ArH).

Found: C, 48.3; H, 2.9; N, 28.9%; M^+, not observed.
$C_{10}H_7N_5OS$ requires: C, 49.0; H, 2.9; N, 28.6%; M, 245.

The Isomerisation of 3-Phenyl-1,2,3-triazolo[1,5-a]-1,3,5-triazin-7(6H)-one-5(4H)-thione (471) to 3-Phenyl-1,2,3-triazolo-[1,5-a]-1,3,5-triazin-5(4H)-one-7(6H)-thione (472)

A mixture of the 1,2,3-triazolo-1,3,5-triazine derivatives (471) and (472) in which the former predominates (0.12 g; 0.0005 mol) was heated under reflux in ethanol (1.0 ml) until all the suspended solid had dissolved. The solid which separated on cooling was collected to give 3-phenyl-1,2,3-triazolo[1,5-a]-1,3,5-triazin-5(4H)-one-7(6H)-thione (472), (0.12 g; 100%) identical (m.p. and i.r. spectrum) to a sample prepared before.

2-(α-Acetoxybenzyl)-1,3,5-triazin-4(5H)-one-6(1H)-thione (476b)

A solution of the 1,2,3-triazolo-1,3,5-triazine (472) (0.37 g, 0.0015 mol) in glacial acetic acid (10.0 ml) was heated under reflux for 2 h. The mixture was evaporated and co-evaporated with toluene and the gummy residue was triturated with ethyl acetate to give a colourless solid which was combined with further material obtained by evaporating the ethyl acetate

mother liquor and retriturating the residue with methylene chloride to give the acetoxybenzyltriazine (476b), (0.20 g, 48%) ν_{max} 1760 and 1680 (CO) cm^{-}, $\delta[(CD_3)_2SO]$ 12.79 (1H, s, NH), 7.60-7.30 (5H, m, ArH), 6.18 (1H, s, benzylic CH)and 2.15 (3H, s, CH_3) and M^+, 277. This compound defied attempted recrystallisation and therefore no elemental analyses were obtained.

Evaporation of the methylene chloride mother liquor gave a yellow froth (0.12 g) whose t.l.c. in ethyl acetate over silica showed it to be a close-running three component mixture containing the acetoxy-compound (476b). The froth was not further investigated.

Acetyl Isocyanate

Acetyl isocyanate was prepared according to the method of Bonte, Druet and Etienne[185] and had b.p. 80-82°/760mmHg (lit.,[185] b.p. 80-82°) and n_D^{18} 1.3974 (lit.,[185] n_D^{25} 1.4032).

Acetyl Isothiocyanate

Acetyl isothiocyanate was prepared by following the conditions of Hirai, Matsui and Takamizawa[186] and had b.p. 80-83°/760mmHg (lit.,[186] b.p. 39.5-40.5/21mmHg).

The Attempted Reaction of 5-Amino-4-phenyl-1H-1,2,3-triazole (468) with Acetyl Isothiocyanate

A solution of the aminotriazole (468) (0.32 g; 0.002 mol) in dry 1,2-dimethoxyethane (10.0 ml) was treated with acetyl isothiocyanate (0.22 g, 0.0022 mol) and the mixture was stirred

at room temperature for 22 h. A second portion of acetyl isothiocyanate was added and stirring was continued for a further 4 h. During this time the colour of the mixture deepened from a pale yellow to a very dark green colour.

Evaporation of the mixture gave a green foam (0.49 g) whose t.l.c. in ethyl acetate over silica showed it to contain at least six components. Attempted separation of the foam by flash chromatography failed only impure multicomponent gums being obtained.

N-Acetyl-N'-(4-phenyl-1H-1,2,3-triazol-5-yl)urea (478a)

A solution of the aminotriazole (468), (0.32 g, 0.002 mol) in dry 1,2-dimethoxyethane (10.0 ml) was treated with acetyl isocyanate (0.19 g, 0.0022 mol) and the mixture was stirred at room temperature for 4 h. Filtration afforded a solid which was combined with a second crop obtained by evaporating the filtrate and triturating the fawn gummy residue with toluene-ethyl acetate to give the urea (478a) (0.36 g; 73%) which formed colourless needles, m.p. 215-218° (from ethanol), ν_{max} 3240 and 3140 (NH) and 1730 and 1700 (CO) cm^{-1}, δ[$(CD_3)_2SO$] 10.78 (1H, bs, NH), 10.19 (1H, bs, NH), 7.80-7.60 (2H, m, ArH), 7.50-7.35 (3H, m, ArH) and 2.12 (3H, s, CH_3).

Found: C, 53.8; H, 4.6; N, 28.8%; M^+, 245.
$C_{11}H_{11}N_5O_2$ requires: C, 53.9; H, 4.5; N, 28.6%; M, 245.

Evaporation of the toluene-ethyl acetate mother liquor gave an amber oil (0.10 g) whose t.l.c. in ethyl acetate over silica showed it to contain four components including the aminotriazole (468) and the urea (478a). The oil was not separated.

N-Acetyl-N'-(1-acetyl-4-phenyl-1H-1,2,3-triazol-5-yl)urea (478b)

The urea (478a) (0.25 g, 0.001 mol) was treated dropwise with acetic anhydride (0.5 ml) and the pasty mixture was heated at 100° (water-bath) for 20 min during which time the solid was never completely in solution. The mixture was cooled and diluted with ether to give a colourless solid which was crystallised to afford N-acetyl-N'-(1-acetyl-4-phenyl-1H-1,2,3-triazol-5-yl)urea (478b), (0.25 g; 89%) which formed colourless needles, m.p. 187-189° (from ethanol), ν_{max} 3240 and 3170 (NH) and 1755, 1730 and 1690 (CO) cm^{-1}, $\delta[(CD_3)_2SO]$ 10.90 (1H, bs, NH), 10.67 (1H, s, NH), 7.90-7.40 (5H, m, ArH), 2.76 (3H, s, CH_3) and 2.12 (3H, s, CH_3).

Found: C, 54.1; H, 4.7; N, 24.3%; M^+, 287.
$C_{13}H_{13}N_5O_3$ requires: C, 54.4; H, 4.5; N, 24.4%; M, 287.

The ethereal filtrate was evaporated and co-evaporated with toluene to give a small amount of yellow gum (0.05 g) which was not investigated further.

The Attempted Cyclisation of N-Acetyl-N'-(4-phenyl-1H-1,2,3-triazol-5-yl)urea (478a)

(i) A suspension of the urea (478a) (0.25 g, 0.001 mol) in 25% v/v aqueous ammonium hydroxide (5.0 ml) was heated under reflux for 1.5 h. The mixture was cooled and the solid was collected and combined with further material obtained by acidifying the basic aqueous filtrate to give the unchanged urea (478a) (0.25 g; 100%) identical (m.p. and i.r. spectrum) to an authentic sample.

(ii) A solution of the urea (478a) (0.25 g, 0.001 mol) in anhydrous ethanol (10.0 ml) was treated with a solution of sodium (0.092 g, 0.004 g.atom) in anhydrous ethanol (5.0 ml) and the mixture was heated under reflux for 3 h. The mixture was evaporated and the residue was dissolved in water (10.0 ml). The basic solution was neutralised with 2M aqueous hydrochloric acid and solid sodium acetate and extracted with methylene chloride. Evaporation of the organic extract gave no material.

(iii) The urea (478a) (0.25 g, 0.001 mol) was heated under reflux with 1M aqueous sodium carbonate (5.0 ml) for 1.5 h. The basic solution was cooled and extracted with methylene chloride to give no residue. Neutralisation of the aqueous mother liquor with 2M aqueous hydrochloric acid and concentrated aqueous ammonia (S.G. 0.88) and re-extraction with methylene chloride also gave no material.

(iv) A suspension of the urea (478a) (0.25 g, 0.001 mol) in 2M aqueous hydrochloric acid (5.0 ml) was heated under reflux for 1.5 h during which time the solid dissolved. Extraction of the acidic mixture with methylene chloride gave no residue. The aqueous acidic solution was neutralised with concentrated aqueous ammonia (S.G. 0.88) and re-extracted with methylene chloride to give the aminotriazole (468) (0.06 g; 34%) identical (m.p. and i.r. spectrum) to an authentic sample.

Methyl N-Cyanoformimidate (488)

The cyano-imidate (488) was prepared according to the method of Hosmane and Leonard[187] and had b.p. 86-88°/14mmHg (lit.,[187] 73-75°/3mmHg).

Ethyl N-Ethoxycarbonylformimidate (482)

The ester-imidate (482) was prepared by the method of Faust[188] and had b.p. 78-82°/15mmHg (lit.,[188] 82-83°/17mmHg).

The Reaction of 5-Amino-4-phenyl-1H-1,2,3-triazole (468) with Ethyl N-Ethoxycarbonylformimidate (482)

(i) A solution of the aminotriazole (468), (0.32 g, 0.002 mol) in ethanol (10.0 ml) was treated dropwise with the imidate (482), (0.58 g, 0.004 mol) and the mixture was heated under reflux for 4 h. Evaporation of the mixture gave a brown oil (0.57 g) whose t.l.c. in ether over silica showed it to be a five component mixture. Trituration with methylene chloride gave a colourless solid which was crystallised to yield 5-formamido-4-phenyl-1H-1,2,3-triazole (486), (0.15 g; 39%) as colourless crystals, m.p. 203-206°, ν_{max} 3360-3100 (NH) and 1670 (CO) cm^{-1}.

Found: C, 56.9; H, 4.3; N, 29.4%; M^+, 188.

$C_9H_8N_4O$ requires: C, 57.4; H, 4.3; N, 29.8%; M, 188.

The methylene chloride mother liquor was evaporated to give an orange gum (0.37 g) whose t.l.c. in ethyl acetate over silica indicated a multicomponent gum containing the formamide (486) as the main component. The gum was not further investigated.

(ii) Repetition of the above reaction using dry toluene as the solvent also produced a multicomponent gum from which small amounts of both the starting aminotriazole (468) (16%) and the formamide (486) (12%) were isolated.

7-Amino-3-phenyl-1,2,3-triazolo[1,5-a]-1,3,5-triazine (491)

A solution of the cyano-imidate (488) (50.4 g, 0.6 mol) in methanol (500 ml) was treated with the aminotriazole (468) (48.0 g, 0.3 mol) in portions and the mixture was heated under reflux for 16 h, a fawn solid being precipitated as the reaction proceeded. The fawn solid was collected and combined with further material obtained by evaporating the filtrate and triturating the residue with ether-ethyl acetate to afford 7-amino-3-phenyl-1,2,3-triazolo[1,5-a]-1,3,5-triazine (491), (total 42.0 g; 66%) which formed colourless crystals, m.p. 224° (from methanol-dimethylformamide), ν_{max} 3320-3120 (NH) and 1720 (C=N) cm^{-1}, δ[$(CD_3)_2SO$] 9.14 (2H, bs, NH_2), 8.29 (1H, s, H-5), 8.30-8.20 (2H, m, ArH), 7.60-7.20 (3H, m, ArH).

Found: C, 56.6; H, 3.8; N, 39.5%; M^+, 212.

$C_{10}H_8N_6$ requires: C, 56.6; H, 3.8; N, 39.6%; M, 212.

Evaporation of the ether-ethyl acetate mother liquor yielded an oily residue which was triturated with ethyl acetate to give a small amount of an unidentified solid, ν_{max} 2080 cm^{-1}.

The Attempted Preparation of N-(4-Phenyl-1H-1,2,3-triazol-5-yl) guanidine (494)

(i) A solution of the aminotriazole (468) (0.32 g, 0.002 mol) in absolute ethanol (10.0 ml) was treated with S-methylisothiouronium sulphate (0.28 g, 0.001 mol) and the mixture was heated under reflux for 2 h. Filtration of the cooled mixture removed the unreacted S-methylisothiouronium sulphate (0.25 g; 89%) and evaporation of the filtrate gave the unchanged aminotriazole (468) (0.32 g; 100%) identical (m.p. and i.r. spectrum) to an

authentic sample.

(ii) A suspension of the S-methylisothiouronium sulphate (0.28 g, 0.001 mol) in absolute ethanol (10.0 ml) was treated with a solution of sodium (0.046 g, 0.002 g.atom) in absolute ethanol (5.0 ml) and the mixture was stirred at room temperature for 15 min. Filtration removed sodium sulphate and the filtrate was treated dropwise with a solution of the aminotriazole (468) (0.32 g, 0.002 mol) in absolute ethanol (5.0 ml). The mixture was stirred at room temperature for 1 h then heated under reflux for 2 h. Evaporation of the mixture and trituration of the residual gum with toluene yielded the aminotriazole (468) (0.31 g; 96%) identical (m.p. and i.r. spectrum) to an authentic sample.

(iii) A solution of the aminotriazole (468) (0.32 g, 0.002 mol) in dry acetonitrile (10.0 ml) was treated with cyanamide (0.093 g, 0.0022 mol) and glacial acetic acid (0.12 g, 0.002 mol) and the mixture was stirred at room temperature for 4 h after which time t.l.c. of the mixture indicated no reaction. The solution was therefore heated under reflux for 2 h then evaporated and the resulting fawn gum triturated with toluene to give a solid (0.36 g) whose i.r. spectrum suggested it was a mixture of the starting materials. Treatment of the solid with water (5.0 ml) removed the cyanamide and left the unchanged aminotriazole (468) (0.16 g; 51%) identical (m.p. and i.r. spectrum) to an authentic sample.

Work-up of the aqueous mother liquor gave no further material.

(iv) A solution of the amine (468) hydrochloride (0.39 g, 0.002 mol) [prepared by treating the aminotriazole (468) with methanolic hydrogen chloride] in absolute ethanol (10.0 ml) was

treated with cyanamide (0.093 g, 0.0022 mol) and the mixture was heated under reflux for 3 h. The mixture was evaporated, treated with water (10.0 ml) and extracted with methylene chloride to give the unreacted aminotriazole (468) (0.08 g; 25%) identical (m.p. and i.r. spectrum) to an authentic sample.

Work up of the aqueous mother liquor gave no further material.

(v) A solution of the amine (468) hydrochloride (0.28 g, 0.0014 mol) in water (5.0 ml) was treated with a solution of cyanamide (0.06 g, 0.0014 mol) in water (5.0 ml) and the mixture was left at room temperature for 28 h. The insoluble solid was collected and combined with a second crop which separated from the filtrate on neutralisation with concentrated aqueous ammonia (S.G. 0.88) and glacial acetic acid to give the unreacted aminotriazole (468) (total 0.16 g; 70%) which was identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

The Attempted Acetylation of 7-Amino-3-phenyl-1,2,3-triazolo-[1,5-a]-1,3,5-triazine (491)

(i) The triazolotriazine (491) (0.21 g, 0.001 mol) was treated dropwise with acetic anhydride (0.5 ml) and the resulting pasty mixture was heated at 100° (water-bath) for 10 min. The solid did not dissolve and the mixture was allowed to cool slowly, diluted with ether and filtered to give unchanged starting-material (491) (0.17 g; 79%) identical (m.p. and i.r. spectrum) to an authentic sample.

The ethereal filtrate was evaporated, treated with water (5.0 ml) and neutralised with 2M aqueous sodium hydroxide and solid sodium acetate. Extraction with methylene chloride gave

no further material.

(ii) The triazolotriazine (491) (0.16 g, 0.00075 mol) was treated with acetic anhydride as in (i) before and the pasty mixture was treated with concentrated sulphuric acid to give a yellow solution. The mixture was left at room temperature for 20 min then treated with ice (2.0 g) and the resulting solid collected and crystallised to give the unreacted starting material (491) (0.08 g; 50%) identical (m.p. and i.r. spectrum) to an authentic sample.

Work-up of the filtrate gave no identifiable material.

The Attempted Diazotization of 7-Amino-3-phenyl-1,2,3-triazolo-[1,5-a]-1,3,5-triazine (491)

(i) A suspension of the triazolotriazine (491) (0.42 g, 0.002 mol) in concentrated hydrochloric acid (0.4 ml) and water (2.0 ml) was treated dropwise with stirring at 0° (ice-salt bath) with a solution of sodium nitrite (0.17 g, 0.0025 mol) in water (1.0 ml) and the mixture was stirred at this temperature for 30 min. The suspended solid did not dissolve. Water (2.0 ml) was added and the mixture was filtered to give unchanged starting-material (491) (0.35 g, 82%) identical (m.p. and i.r. spectrum) to an authentic sample.

Work-up of the acidic aqueous mother liquor gave no further material.

(ii) The triazolotriazine (491) (0.42 g, 0.002 mol) was dissolved in 88% w/v aqueous phosphoric acid (2.0 ml). Gas evolution was observed and after the addition of glacial acetic acid (0.6 ml) the solution was cooled to 0° (ice-salt bath). Sodium nitrite (0.28 g, 0.004 mol) was added in portions and

the mixture was stirred for 10 min then diluted with water (5.0 ml). The acidic solution was neutralised with 2M aqueous sodium hydroxide and glacial acetic acid and extracted with methylene chloride to give no material. The aqueous mother liquor was evaporated and the resulting inorganic cake was heated under reflux with ethyl acetate (50 ml) for 30 min. Evaporation of the ethyl acetate extract gave no material.

(iii) A solution of the triazolotriazine (491) (0.85 g, 0.004 mol) in glacial acetic acid was treated at 0° (ice-salt bath) with a solution of sodium nitrite (2.0 g) in water (12.0 ml). Gas evolution occurred and the mixture was stirred in the melting ice-bath for 2 h then concentrated to about one third of its volume. Filtration gave 2-(α-acetoxybenzyl)-4-amino-1,3,5-triazine (495a), (0.56 g; 58%) which formed colourless needles, m.p. 176-179° (from ethanol-b.p. 80-100° light petroleum), ν_{max} 3360-3300 and 3210-3080 (NH), 1750 (CO) and 1670 (C=N) cm^{-1}, δ($CDCl_3$) 8.51 (1H, s, H-6), 7.60-7.20 (5H, m, ArH), 6.38 (1H, s, benzylic CH), 5.76 (2H, bs, NH_2) and 2.20 (3H, s, CH_3) and [$(CD_3)_2SO$] 8.42 (1H, s, H-6), 7.66 (2H, bs, NH_2), 7.60-7.20 (5H, m, ArH), 6.19 (1H, s, benzylic CH) and 2.14 (3H, s, CH_3).

Found: C, 59.1; H, 5.1; N, 22.9%; M^+, 244.
$C_{12}H_{12}N_4O_2$ requires: C, 59.0; H, 5.0; N, 22.9%; M, 244.

The aqueous mother liquor was further concentrated and extracted with methylene chloride to yield a dark brown oil (0.38 g). Trituration of the oil with ether gave a small amount of a brown solid tentatively identified as N-(2-acetoxy-2-phenylacetyl)-N'-formylurea (497), (0.11 g; 10%) which formed fawn rectangular crystals, m.p. 159-162° (from b.p. 80-100°

light petroleum-ethanol), ν_{max} 3260 and 3160 (NH) and 1750 and 1680 (CO) cm^{-1}.

Found: C, 54.8; H, 4.6; N, 10.5%; M^+, 264.
$C_{12}H_{12}N_2O_5$ requires: C, 54.6; H, 4.6; N, 10.6%; M, 264.

Evaporation of the ethereal mother liquor gave a small amount of brown gum which was not further investigated.

2-(α-Acetoxybenzyl)-4-amino-1,3,5-triazine (495a)

A solution of the triazolotriazine (491) (0.42 g, 0.002 mol) in glacial acetic acid (10.0 ml) was heated under reflux for 3 h. The mixture was evaporated and co-evaporated with toluene to give 2-(α-acetoxybenzyl)-4-amino-1,3,5-triazine (495a), (0.46 g; 95%) identical (m.p. and i.r. spectrum) to a sample prepared previously.

4-Amino-2-(α-chlorobenzyl)-1,3,5-triazine (495b)

(i) The triazolotriazine (491) (0.42 g, 0.002 mol) was dissolved in glacial acetic acid (10.0 ml) and acetyl chloride (30.0 ml). Gas evolution occurred and the mixture was heated under reflux for 3 h, then evaporated and co-evaporated with toluene to give a yellow gum (0.42 g). Trituration of the gum with ether afforded a colourless solid which was combined with a second crop obtained by evaporating the ethereal mother liquor and re-triturating the resulting gum with toluene-b.p. 40-60° light petroleum to give 4-amino-2-(α-chlorobenzyl)-1,3,5-triazine (495b), (total 0.22 g; 73%) which formed irregular colourless crystals, m.p. 128-130° (from toluene), ν_{max} 3360-3300 and 3220-3100 (NH) and 1670 (C=N) cm^{-1}, $\delta(CDCl_3)$ 8.57 (1H, s, H-6), 7.60-7.10 (5H, m, ArH), 5.76 (1H, s, benzylic CH) and 5.66 (1H, bs, NH).

Found: C, 54.7; H, 4.2; N, 25.5%; M^+, 222/220.
$C_{10}H_9ClN_4$ requires: C, 54.4; H, 4.1; N, 25.4%; M, 220.5.

Evaporation of the toluene-light petroleum mother liquor gave a yellow gum (0.12 g) which was not further investigated.

(ii) A suspension of the triazolotriazine (491) (0.42 g, 0.002 mol) in concentrated hydrochloric acid (10.0 ml) was stirred at room temperature for 16 h during which time the suspended solid dissolved. The mixture was poured into water (20.0 ml) and neutralised with 5M aqueous sodium hydroxide. Extraction with methylene chloride gave a fawn froth which could not be solidified in contact with organic solvents and whose t.l.c. in ethyl acetate over silica showed it to be a four component mixture containing none of the chlorobenzyltriazine (495b). The froth was not further investigated.

The Reaction of 4-Amino-2-(α-chlorobenzyl)-1,3,5-triazine (495b) with Sodium Azide in Aqueous Ethanol

(i) A solution of the chloro-compound (495b) (0.44 g, 0.002 mol) in ethanol (10.5 ml) was heated under reflux with a solution of sodium azide (0.26 g, 0.004 mol) in water (4.5 ml) for 1.5 h, the initially yellow solution deepening in colour to a bright orange during this time. On cooling, the solution deposited a fawn solid which was collected to afford 4-amino-2-benzoyl-1,3,5-triazine (505), (0.25 g; 62%) which formed lemon needles, m.p. 230-233° (from ethanol-water), ν_{max} 3360-3140 (NH), 1715 (CO) and 1690 (C=N) cm^{-1}, δ[$(CD_3)_2SO$] 8.62 (1H, s, H-6) and 8.00-7.40 (5H, m, ArH).

Found: C, 60.2; H, 4.2; N, 28.6%; M^+, 200.06962.
$C_{10}H_8N_4O$ requires: C, 60.0; H, 4.0; N, 28.0%; M, 200.06981.

The ethanolic filtrate was evaporated and the residue was treated with water (5.0 ml) and extracted with methylene chloride to give a small amount (0.07 g) of an unidentified fawn solid.

4-Amino-2-benzoyl-1,3,5-triazine Oxime (508a)

A solution of the ketone (505) (0.20 g, 0.001 mol) in ethanol (10.0 ml) was treated with hydroxylamine hydrochloride (0.14 g, 0.002 mol) followed by anhydrous sodium acetate (0.25 g, 0.003 mol) and the mixture was heated under reflux for 5 h. The mixture was evaporated and the residue was treated with water (5.0 ml) and filtered to yield the oxime (508a), (0.18 g; 82%) which formed colourless cubes, m.p. 235-238° (from ethanol-dimethylformamide), ν_{max} 2360-2260 and 2200-2100 (NH) and 1660 (C=N) cm^{-1}, $\delta[(CD_3)_2SO]$ 11.95 (1H, bs, oxime OH), 8.45 (1H, s, H-6), 7.60 (2H, bs, NH_2) and 7.35 (5H, s, ArH).

Found: M^+, 215.08062.

$C_{10}H_9N_5O$ requires: M, 215.08070.

Work-up of the aqueous mother liquor gave no further material.

4-Amino-2-benzoyl-1,3,5-triazine Hydrazone (508b)

The ketone (505) (0.20 g, 0.001 mol) was heated under reflux with 100% hydrazine hydrate (0.05 g, 0.001 mol) in methanol (10.0 ml) for 3 h. The solution was cooled and the deposited solid was collected and combined with further material obtained by evaporating the filtrate and triturating the residue with ether to afford the hydrazone (508b), (total 0.19 g; 90%)

which formed colourless plates, m.p. 208-211° (from ethanol-dimethylformamide), ν_{max} 3360, 3240 and 3160 (NH) and 1650 (C=N) cm^{-1}, δ[$(CD)_3SO$] 8.26 (1H, s, H-6), 7.60-7.00 (9H, m, 4NH and ArH).

Found: C, 56.0; H, 4.8; N, 38.7%; M^+,214.09653.
$C_{10}H_{10}N_6$ requires: C, 56.1; H, 4.7; N, 39.2%; M, 214.09669.

4-Amino-2-benzoyl-1,3,5-triazine Phenylhydrazone (508c)

A solution of the ketone (505) (0.20 g, 0.001 mol) in methanol (10.0 ml) was treated with phenylhydrazine (0.11 g, 0.001 mol) and toluene-p-sulphonic acid (0.01 g) and the mixture was heated under reflux for 3 h. The mixture was cooled and the solid was collected and combined with a second crop obtained by evaporating the filtrate and triturating the residue with ether to give the phenylhydrazone (508c) (total 0.28 g; 97%) which formed bright yellow needles, m.p. 226-228° (from ethanol-dimethylformamide-water), ν_{max} 3450, 3360-3260 and 3240-3140 and 1635 (C=N) cm^{-1}, δ[$(CD_3)_2SO$] 8.60 (1H, s, H-6), 7.99 (1H, bs, NH), 7.85 (1H, bs, NH), 7.60-7.10 (10H, m, ArH) and 6.92 (1H, bs, NH).

Found: M^+, 290.12809.
$C_{16}H_{14}N_6$ requires: M, 290.12799.

Ethyl Acetimidate Hydrochloride

Ethyl acetimidate hydrochloride was prepared (yield 84%) by the method of Peters and Schaefer[189] and had m.p. 112-113° (lit.,[189] 110-115°).

Ethyl Acetimidate

Ethyl acetimidate was prepared from ethyl acetimidate hydrochloride as described by Peters and Schaefer[189] and was obtained as a clear oil (yield 52%), $\delta(CDCl_3)$ 7.00-5.00 (1H, bs, NH), 4.00 (2H, q, J7Hz, CH_2), 1.93 (3H, s, CH_3) and 1.15 (3H, t, J7Hz, CH_3).

N-(4-Phenyl-1H-1,2,3-triazol-5-yl)acetamidinium Acetate (515)

A solution of the aminotriazole (468) (16.0 g, 0.01 mol) in dry acetonitrile (400 ml) was treated dropwise with stirring with ethyl acetimidate (17.6 g, 0.02 mol) followed by glacial acetic acid (6.0 g, 0.01 mol) and the mixture was stirred at room temperature for 5 h. Filtration of the resulting suspension afforded N-(4-phenyl-1H-1,2,3-triazol-5-yl)acetamidinium acetate (515), (17.3 g; 66%) which formed colourless crystals, m.p. 122-123° (from ethyl acetate), ν_{max} 2800-2300br ($\overset{+}{N}H$) and 1660 (C=N) cm^{-1}, $\delta[(CD_3)_2SO]$ 10.00-7.80 (4H, bs, 4NH), 8.25-8.15 (2H, m, ArH), 7.50-7.25 (3H, m, ArH), 2.08 (3H, s, CH_3) and 1.90 (3H, s, CH_3).

Found: C, 54.7; H, 6.0; N, 27.1%; M^+, 201 (M-AcOH).
$C_{12}H_{15}N_5O_2$ requires: C, 55.2; H, 5.8; N, 26.8%; M, 261.

Evaporation of the filtrate gave a yellow syrup (11.5 g) which was shown by t.l.c. in ethyl acetate over silica to be a four component mixture containing both the starting aminotriazole (468) and the product (515). The syrup was not further investigated.

N-(4-Phenyl-1H-1,2,3-triazol-5-yl)acetamidine (516)

A solution of the acetamidinium acetate (515) (0.26 g, 0.001 mol) in water (10.0 ml) was treated with solid sodium bicarbonate (0.092 g, 0.0011 mol). Heat was evolved and a colourless solid separated. This was collected and crystallised to afford the acetamidine (516) (0.20 g, 100%) which formed colourless crystals, m.p. 177-180° (from ethanol-b.p. 80-100° light petroleum), ν_{max} 3500, 3390 and 3300-3100 (NH) and 1675 (C=N) cm^{-1}, δ[$(CD_3)_2SO$] 9.00-5.50 (3H, bs, NH), 8.25-8.15 (2H, m, ArH), 7.40-7.30 (3H, m, ArH) and 2.09 (3H, s. CH_3).

Found: C, 59.4; H, 5.5; N, 34.8%; M^+, 201.

$C_{10}H_{11}N_5$ requires: C, 59.7; H, 5.5; N, 34.8%; M, 201.

5,7-Dimethyl-3-phenyl-1,2,3-triazolo[1,5-a]-1,3,5-triazine (517a)

(i) A suspension of the amidinium acetate (515) (10.44 g, 0.04 mol) in triethyl orthoacetate was heated under reflux until the solid had completely dissolved (5 min). On cooling the yellow solution deposited 5,7-dimethyl-3-phenyl-1,2,3-triazolo-[1,5-a]-1,3,5-triazine (517a), (6.90 g; 77%) which formed lemon needles, m.p. 160-162° (from b.p. 80-100° light petroleum), δ($CDCl_3$) 8.43-8.31 (2H, m, ArH), 7.60-7.35 (3H, m, ArH), 3.09 (3H, s, CH_3) and 2.77 (3H, s, CH_3); heating to 97° caused coalescence of the methyl proton resonances to a singlet at δ2.87.

Found: C, 63.6; H, 5.0; N, 31.1%; M^+, 225.

$C_{12}H_{11}N_5$ requires: C, 64.0; H, 4.9; N, 31.3%; M, 225.

Evaporation of the triethyl orthoacetate mother liquor gave

an orange residue (1.28 g) which was shown by t.l.c. in ethyl acetate over silica to be a six component mixture containing further product. This material was not further investigated.

(ii) A suspension of the amidinium acetate (515) (0.39 g, 0.0015 mol) in triethyl orthoacetate (20.0 ml) was heated under reflux for 2 h the suspended solid dissolving completely during the first few minutes. The excess triethyl orthoacetate was removed under reduced pressure (oil pump) and the residual semi-solid was flash chromatographed over silica. Elution with methylene chloride-ethyl acetate (1:1) gave the triazolotriazine (517a), (0.16 g; 47%) identical (m.p. and i.r. spectrum) to a sample prepared as in (i) before.

Further elution with ethyl acetate produced only multi-component gums which were not further investigated.

(iii) Repetition of the reaction as in (ii) but with heating under reflux for 20 min gave the triazolotriazine (517a) (59%), identical (m.p. and i.r. spectrum) to an authentic sample, together with multicomponent gums.

(iv) Repetition of the reaction as in (ii) but with stirring at room temperature for 19 h gave only the unreacted starting material in quantitative yield.

(v) A solution of the acetamidine (516) (0.20 g, 0.001 mol) in triethyl orthoacetate (10.0 ml) was heated under reflux for 2 h. As the t.l.c. of the mixture after this time indicated that no reaction had occurred toluene-p-sulphonic acid (0.01 g) was added and the heating was continued for a further 5 h. The mixture was evaporated under reduced pressure (oil pump) and the resulting yellow gum was flash chromatographed over silica.

Elution with methylene chloride-ethyl acetate (1:1) yielded

a gummy yellow solid (0.10 g) which was recrystallised from b.p. 80-100° light petroleum to give the triazolotriazine (517a) (0.04 g; 16%) identical (m.p. and i.r. spectrum) to an authentic sample.

Evaporation of the crystallization mother liquor gave a yellow gum (0.02 g) which was shown by t.l.c. in ethyl acetate over silica to be a three component mixture containing more product. No attempt was made to separate the gum.

Further elution gave only multicomponent oils or gums.

5-Methyl-3-phenyl-1,2,3-triazolo[1,5-a]-1,3,5-triazine (517b)

(i) A suspension of the acetamidinium acetate (515), (0.52 g, 0.002 mol) in triethyl orthoformate (20.0 ml) was heated under reflux for 1 h during which time the colourless solid dissolved to give a yellow solution. The mixture was evaporated under reduced pressure (oil pump) and the residue was triturated with ether to give 5-methyl-3-phenyl-1,2,3-triazolo[1,5-a]-1,3,5-triazine (517b), (0.057 g; 14%) which formed yellow needles, m.p. 159-162° (needles to plates 119-123°) (from b.p. 80-100° light petroleum) $\delta(CDCl_3)$ 8.69 (1H, s, H-7), 8.45-8.30 (2H, m, ArH), 7.65-7.35 (3H, m, ArH) and 3.16 (3H, s, CH_3).

Found: 211.08449

$C_{11}H_9N_5$ requires: 211.08579

Evaporation of the filtrate gave an orange oil (0.44 g) which was shown by t.l.c. in ethyl acetate over silica to be a multicomponent mixture. Attempted separation of the oil by flash chromatography failed only multicomponent gums being obtained.

(ii) Repetition of the reaction (i) with heating only until all of the suspended solid had dissolved (1-2 min) gave on cooling and filtration the unchanged starting material (515) (0.06 g; 11%) identical (m.p. and i.r. spectrum) to an authentic sample.

Evaporation of the filtrate gave a red oil (0.42 g) whose t.l.c. indicated it to be a multicomponent mixture. Attempted separation of the oil by flash chromatography gave only multicomponent gums.

The Attempted Reaction of the Acetamidine (516) with Triethyl Orthoformate

A solution of the acetamidine (516) (0.40 g, 0.002 mol) in triethyl orthoformate (10.0 ml) was heated under reflux for 4 h. Removal of the excess ortho-ester under reduced pressure (oil pump) yielded a crimson gum (0.60 g) whose t.l.c. in methylene chloride-ethyl acetate (1:1) over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

2-(α-Acetoxybenzyl)-4,6-dimethyl-1,3,5-triazine (523a)

A solution of the triazolotriazine (517a), (0.45 g, 0.002 mol) in glacial acetic acid (10.0 ml) was heated under reflux for 1 h. Evaporation of the mixture and co-evaporation with toluene yielded an orange oil (0.61 g) which was flash chromatographed over silica. Elution with methylene chloride-ethyl acetate (1:1) yielded 2-(α-acetoxybenzyl)-4,6-dimethyl-1,3,5-triazine (523a), (0.38 g; 74%) which formed colourless rhombic

crystals, m.p. 118-120° (from b.p. 80-100° light petroleum), ν_{max} 1735 (CO) cm^{-1}, $\delta(CDCl_3)$ 7.60-7.25 (5H, m, ArH), 6.49 (1H, s, benzylic CH), 2.58 (6H, s, $2CH_3$) and 2.21 (3H, s, CH_3).

Found: C, 65.2; H, 5.9; N, 16.5%; M^+, 257.

$C_{14}H_{15}N_3O_2$ requires: C, 65.4; H, 5.8; N, 16.3%; M, 257.

2-(α-Chlorobenzyl)-4,6-dimethyl-1,3,5-triazine (523b)

(i) The triazolotriazine (517a) (4.50 g, 0.02 mol) was added in portions to a stirred mixture of acetyl chloride (90.0 ml) and glacial acetic acetic acid (30.0 ml). Gas evolution occurred and after stirring for 2 h the mixture was evaporated and co-evaporated with toluene under high vacuum (oil pump) to give a pale yellow oil (5.03 g) which was separated by flash chromatography over silica. Elution with methylene chloride-ethyl acetate (1:1) yielded 2-(α-chlorobenzyl)-4,6-dimethyl-1,3,5-triazine (523b), (3.92 g; 84%) as a colourless oil, b.p. 150°/1mmHg, $\delta(CDCl_3)$ 7.70-7.55 (2H, m, ArH), 7.40-7.25 (3H, m, ArH), 5.91 (1H, s, benzylic CH) and 2.61 (6H, s, $2CH_3$).

Found: 233.07299

$C_{12}H_{12}ClN_3$ requires: 233.07197

Further elution gave the acetoxybenzyltriazine (523a) (0.29 g; 6%) identical (m.p. and i.r. spectrum) with a sample prepared before.

(ii) The triazolotriazine (517a) (0.45 g, 0.002 ,ol) in concentrated hydrochloric acid (10.0 ml) was stirred at room temperature for 17 h. The mixture was diluted with water (10.0 ml), neutralised with 5M aqueous sodium hydroxide and solid sodium acetate and extracted with methylene chloride to give a

clear gum (0.30 g). Trituration of the gum with methylene chloride afforded a colourless solid which was combined with a second crop obtained by evaporating the methylene chloride mother liquor and flash chromatography in cyclohexane-ethyl acetate (1:1) over silica of the resulting gum to give the aminotriazole (468) (total 0.17 g; 53%) identical (m.p. and i.r. spectrum) to an authentic sample.

The Reaction of 2-(α-Chlorobenzyl)-4,6-dimethyl-1,3,5-triazine (523b) with Sodium Azide in Aqueous Ethanol

(i) A solution of the chloro-compound (523b) (0.23 g, 0.001 mol) in ethanol (7.0 ml) was treated with a solution of sodium azide (0.13 g, 0.002 mol) in water (3.0 ml) and the mixture was heated under reflux for 2 h. The mixture was evaporated, the residue was treated with water (5.0 ml) and the solution was extracted with methylene chloride to afford an orange gum (0.12 g) whose t.l.c. indicated that it was an inseparable multicomponent mixture. The gum was not further investigated.

(ii) A solution of the chloro-compound (523b) (0.23 g, 0.001 mol) in ethanol (7.0 ml) was mixed with a solution of sodium azide (0.26 g, 0.004 mol) and the mixture was stirred at room temperature for 17 h. The ethanol was evaporated at room temperature and the oily residue was treated with water (5.0 ml) and extracted with methylene chloride to give a colourless oil (0.21 g) which was shown (i.r. and ^{1}H n.m.r. spectrum) to be a 3:2 mixture of the unreacted chloro-compound (523b) and the desired azide (525). The mixture could not be separated.

(iii) A solution of the chloro-compound (523b) (0.23 g, 0.001 mol) in ethanol (7.0 ml) was treated with a solution of

sodium azide (0.52 g, 0.008 mol) in water (3.0 ml) and the mixture was stirred at room temperature for 24 h. The ethanol was evaporated at room temperature and the residue was treated with water (5.0 ml) and extracted with methylene chloride to give a colourless oil (0.20 g). The oil was flash chromatographed in methylene chloride-ethyl acetate (9:1) over silica to afford 2-benzoyl-4,6-dimethyl-1,3,5-triazine (524), (0.19 g, 63%) which formed fawn crystals, m.p. 76-77° (from b.p. 80-100° light petroleum), ν_{max} 1690 (CO) cm^{-1}, $\delta(CDCl_3)$ 8.05-7.90 (2H, m, ArH), 7.65-7.35 (3H, m, ArH) and 2.72 (6H, s, $2CH_3$).

Found: C, 68.1; H, 5.1; N, 19.6%; M^+, 213.

$C_{12}H_{11}N_3O$ requires: C, 67.6; H, 5.2; N, 19.7%; M, 213.

GENERAL EXPERIMENTAL DATA

Infra-red spectra were recorded on Perkin-Elmer 157G, 298 or 781 instruments and bands were strong and sharp unless specified w as weak or br as broad. Solids were measured as nujol mulls and liquids as liquid films.

^{1}H N.m.r. spectra were recorded at 80MHz on a Bruker WP80 instrument, at 100MHz on a Varian HA100 instrument, at 200MHz on a Bruker WP200 instrument or at 360MHz on a Bruker WH360 instrument while ^{13}C n.m.r. spectra were measured at 90MHz on a Bruker WH360 instrument. Bands were sharp unless specified b as broad; s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. TMS (Tetramethylsilane) was used as an internal standard on spectra recorded at 100MHz.

Mass spectra were measured at 70eV on an A.E.I. MS902 instrument which was operated by Mr. D. Thomas, Department of Chemistry, University of Edinburgh and microanalyses were performed by Mr. J. Grunbaum, Department of Chemistry, University of Edinburgh. Melting points were determined on a Kof ler hot-stage microscope and are uncorrected.

All organic extracts were dried over anhydrous magnesium sulphate prior to evaporation.* Solvents were of technical grade unless otherwise specified and light petroleum had b.p. 60-80° except where stated.

Column chromatography and thin layer chromatography was carried out over silica (Merck 7730) or alumina (Merck 1068) and components were visualized under U.V. light. Flash chromatography was carried out over silica (Merck 9385).

(* under reduced pressure)

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